Guide to the Inpatient Pain Consult

Alaa Abd-Elsayed
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To my parents, my wife, and my two beautiful kids, Maro and George.

Preface

The inpatient pain consult service has become a crucial service in modern medicine and an essential service for the hospitalized patient. Hospitalized patients may experience pain related to acute and chronic conditions. These patients may simultaneously possess medical comorbidities that can significantly impact the utility or appropriateness of certain analgesic modalities. In addition, these patients may acutely present for hospitalized care with limited information available to align inpatient analgesic care with what is being provided in the outpatient setting.

The impetus and intention of this book is to serve as a guide for different specialties providing care for patients suffering from pain in the inpatient setting. This book discusses the most common scenarios that complicate pain management for these patients including, but not limited to, patients with organ failure impacting metabolism and excretion of various medications, patients with implanted devices to treat pain, critically ill patients in the Intensive Care Unit (ICU), patients with tolerance/addiction, patients with psychological conditions, and special populations as children, elderly, and prisoners.

I would like to thank all the authors who contributed to this book, the publisher (Springer) who made this work possible and my family for supporting me in my efforts to complete this task.

Madison, WI, USA — Alaa Abd-Elsayed

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Chapter 1
General Concepts

Adam Weinstein and Alaa Abd-Elsayed

1.1 Introduction

The chronic pain patient poses numerous challenges to the clinician. Chronic pain affects as much as 30% of adults in the USA [1]. Challenges range from refractory pain control, complex pre-existing pain conditions superimposed with acute pain stemming from a hospital admission, polypharmacy, communication barriers, genetic profiles and drug response, psychological barriers, coping mechanisms, and the ever-present opioid epidemic. In order to treat the patient effectively one must take a comprehensive and thorough approach, which includes classification of pain, assessment of pain, measurement of pain, treatment, and finally the reassessment of pain or follow-up evaluation.

1.2 Initial Pain Evaluation and Diagnosis

Firstly, one must establish with a patient what are the exact components of pain. By definition pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." [2] Because pain is a subjective experience it is difficult to describe and has layers of complexity that make formulation of an effective treatment plan difficult [3, 4]. Physiological signs such as heart rate and blood pressure or behavioral ques. such as facial expressions are not always accurate or specific [3, 4]. The best indicator of pain is a patients self-described description of their pain. In order to ascertain a useful enough description to guide therapy a complete history and physical is mandatory.

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Overall the clinician must observe the general appearance of the patient and look for any overt deformities or abnormalities or manifestations of systemic disease. When inspecting the perceived pain location, the skin color should be noted, associated tenderness with palpation, pain response to pin prick and light touch, and pain response to changes in temperature using ice or heat. As part of the physical exam extra consideration should be taken for a full assessment of the musculoskeletal and neurological systems [1, 5]. When assessing the neurological system, it is essential to perform a basic screening exam: cranial nerves, spinal nerves, and mental status. After this specific dermatomes and sensory tests, muscle/motor tests can be performed based on the type of pain the patient elicits [5]. With respect to the musculoskeletal system it is important to assess range of motion, body posture, habitus, spine curvature, limb deformities, muscle contour, tone, signs of atrophy and hypertrophy [5].

Information that must also be gleaned from the patient includes pain characteristics, past treatment success and failures, relevant medical conditions and family history, psychosocial history, impact of pain on daily life, and establishment of patient goals and expectations [1, 3, 4].

While comprehensive, Turk and Meichenbaum propose that in order to take an appropriate pain inventory three questions should guide the clinical assessment. What is the extent of disease? What is the magnitude of suffering? Is the behavior appropriate to the disease or injury? [6] The combination of these two approaches, a systematic history, and answering the above questions will guide an accurate patient assessment assuming no barriers are present (such as inability to communicate, delirium, etc.)

Once a history has been obtained the data from the patient can then be used to determine if additional diagnostic testing is required, if the working diagnosis explains the pain symptoms in questions, or if enough information has been acquired to begin pain treatment [1]. After a proper pain inventory has been achieved and the patient and clinician develop a rapport, goals can be established, and treatment may commence.

1.3 Treatment

Treatment can be stratified into multiple categories: medications, pain psychology, physical medicine, interventional pain, alternative approaches, and surgical treatment. Kamper et al. demonstrated in 2015 that using these categories to form a multidisciplinary approach to tackle pain is more effective in treating both pain overall as well as measurable outcomes such as returning to work [7].

Medication should not be the only option that is offered to patients but be used in conjunction with the other modalities. However, if indicated there are a variety of medications that can be used that are not opioid based. These options include: NSAIDS, steroids, alpha 2 agonists, antidepressants, antiepileptics, muscle relaxants, NMDA receptor antagonists, topical agents and creams [8]. It is important to

understand the effect of medications on different disease conditions as some pain medications can be harmful in certain situations e.g. NSAIDs can worsen Kidney disease in patients with kidney failure.

In addition to pharmacologic techniques are also the nonpharmacologic. A TENS unit is a form of transcutaneous electric nerve stimulation that aids to temporarily relieve pain during application and be used both in the hospital and taken home [9]. Other nonpharmacologic forms of pain management include cold therapy and heat therapy. Cold therapy includes ice packs, chemical gel packs, or vaper sprays [10]. Heat therapy can be applied to control pain by altering local blood flow and inducing vasodilation. For severe pain the above therapies should be combined with regional anesthesia, and a short term (ideally less than 3 days) opioid regimen. When selecting an opioid, the length of action, metabolism, and side effects must be considered. This is because pharmacokinetics and metabolism may be altered in the inpatient setting and side effects such as renal clearance may be altered resulting in significant comorbidity [11].

Regional anesthesia and pain blocks at the level of the nerve fibers leads to definite reduction in the amount of medications and opioids needed. Catheters can be left in place and an infusion started so that long term pain relief can be achieved [12].

In addition to the physical approach to managing pain symptoms the emotional and psychological components of pain must also be addressed. It is very valuable to have an integrative medicine service that can see complex pain patients in order to address issues such as: coping mechanisms, pain psychology, mindfulness, relaxation exercises, meditation, and more [13, 14]. This approach offers a complete package in addressing pain as a global body problem and can extend beyond the inpatient stay and be used as maintenance for persistent pain control strategies.

Overall, using multiple modalities in treating pain is very advisable to both reduce the need for opioids and improve pain control.

1.4 Pain Assessment Tools

Information must be acquired from the patient and this includes characteristics of pain and assessment of pain in patients with communication barriers especially relevant to the inpatient setting. The following tables summarize the strategies to diagnose and assess pain for the inpatient (Tables 1.1 and 1.2).

Table 1.1 Pain characteristics [15]

Pain characteristics	
Location	Site, referred, deep, superficial, course, pattern
Duration/frequency	Brief, long, intermittent, recurrent, rhythmic, constant, refractory, fluctuating
Quality	Burning, aching, prickling, sharp, dull, jabbing, electrical, squeezing
Associated symptoms	Hypersensitivity, vomiting, visceral, sweating, trophic changes

Table 1.2 Tools to overcome communication barriers [3, 4]

Tools to assess pain in patients with communication challenges: elderly, infants, critically ill, cognitive deficiency, language differences	
Take the necessary time	Use pain rating scales
Self report	Painful ailments (example rib fractures)
Pain behaviors	Physiological measures

In addition to the above tables the unidimensional tools such as the NRS (Numerical rating scale) and the VAS (Visual analog scale) are excellent measures of pain. This not only allows the patient to establish a baseline pain reference but with continued evaluation and reexamination after treatment changes trends of pain can be established objectively [16].

Other tools available to the clinician are multidimensional tools. These tools not only asses pain characteristics but also pain impact. Of the various tools: Initial Pain Assessment, Brief Pain Inventory (BPI), and McGill Pain Questionnaire (MPQ) the BPI has special utility. The BPI has two forms: a long 17 questions survey and a short 9 question form. The BPI is one of the most commonly used pain assessment tools. The short form is most frequently used [17]. The BPI has shown to have excellent reliability for both pain intensity and life pain interference [18]. The BPI captures aspects of pain management such as site of pain but also response to pain treatment and medication in a reliable, accurate, tested, and clinically useful way [17–19].

1.5 Challenges in Management of Pain While in the Hospital

The chronic pain patient poses numerous challenges. In particular patients who suffer from non-cancerous chronic pain. These factors are a result of medication tolerance, medication induced hyperalgesia, central sensitization, practice environments, and communication barriers, to name a few [20].

Chu et al. showed that in patients taking opioids, tolerance and hyperalgesia were especially important in that it limits the clinical utility of opioids and thus treating or controlling baseline and acute on chronic pain [21]. Gardell et al. demonstrates the paradoxical effect of repeated opioid doses and pain control and resultant hypersensitivity, increased excitability, and morphine induced elevation of spinal dynorphin content [20]. In those taking methadone for maintenance of pain control or addiction Compton et al. and Doverty et al. demonstrated that there is a dramatic intolerance to new pain due to the central effect of opioid hyperalgesia [22, 23].

The above demonstrates the impact of central sensitization. However, endogenous mechanisms are not the only challenges that these patients face. There are both clinical and system wide issues that add to the complexity of these patients. From a clinical standpoint, a lack of experience can lead to patient treatment inadequacies.

Additionally, it is easy to assume a person is just "a drug seeker." Complicating this picture is the fact that many of these patients may be addicted to their pain regimen, have fears about not getting adequate treatment, or have underlying psychiatric issues that further confound treating and diagnosing this patient group.

At the system wide level, a new wave of opioid regulation strategies has been employed in USA. This has led to opioid restrictive practices, fear based medical practice, and numerous concerns about care providers ability to practice in this new climate. This ultimately can result in patients feeling like doctors have abandoned their treatment or not taking pain complaints seriously. This further strengthens the point of view of a multi modal and multi-disciplinary approach to treating chronic pain.

1.6 Management of Pain in the Inpatient Setting

When deciding on an appropriate treatment plan for patients with chronic pain while in the hospital there are a variety of tools and services that should be utilized. As described earlier these options range from integrative medicine, to medical management, to pain interventions. Decisions should be made based on the thorough history and physical and supported be clinical evidence and patient described efficacy, successes, or failures. Thus, a multimodal approach is the best way to tackle all of the features that pain typically presents from psychological to physical, and finally supportive.

For mild to moderate pain patients should be treated with NSAIDS, steroids, alpha 2 agonists, antidepressants, antiepileptics, muscle relaxants, NMDA receptor antagonists, topical agents and creams [8]. In addition to medications non-medication approaches can also be helpful in mild to moderate pain. A TENS unit is a form of transcutaneous electric nerve stimulation that aids to temporarily relieve pain during application and be used both in the hospital and taken home [9]. Other nonpharmacologic forms of pain management include cold therapy and heat therapy. Cold therapy includes ice packs, chemical gel packs, or vaper sprays. This can help with edema and inflammatory related pain [10]. Heat therapy can be applied to control pain by altering local blood flow and inducing vasodilation. Some can even be impregnated with capsaicin to aide in pain reduction [10]. When the above therapies have been tried or do not provide useful results they can be continued in conjunction with more aggressive means of treatment.

For refractory pain and for severe pain the above therapies should be combined with regional anesthesia, and a short term (ideally less than 3 days) opioid regimen. Depending on the site of pain ultrasound guidance can aide in nerve blocks that can over hours of relief. However, if the pain is continuous and refractory opioids may be necessary. When selecting an opioid, the length of action, metabolism, and side effects must be considered. This is because pharmacokinetics and metabolism may be altered in the inpatient setting and side effects such as renal clearance may be altered resulting in significant comorbidity [11]. An important consideration is that

when treatment methods are combined with regional anesthesia and pain is blocked at the level of the nerve fibers than there is a definite reduction in the amount of medications and opioids needed. Catheters can be left in place and an infusion started so that long term pain relief can be achieved [12].

In addition to the physical approach to managing pain symptoms the emotional and psychological components of pain must also be addressed. It is very valuable to have an integrative medicine service that can see complex pain patients in order to address issues such as: coping mechanisms, pain psychology, mindfulness, relaxation exercises, meditation, and more [13, 14]. This approach offers a complete package in addressing pain as a global body problem and can extend beyond the inpatient stay and be used as maintenance for persistent pain control strategies.

1.7 Discharge Plan

When discharging a patient from an inpatient admission the pain trend should be tracked and reviewed over the course of the hospitalization. This allows formulation of an appropriate medication discharge regimen. In accordance with the level of pain and the amount of medication over a patient's baseline home regimen an appropriate weaning protocol should be devised. Lastly follow up in the pain clinic should occur regularly until the patient has returned to their baseline level of pain at the minimum with a goal of overall pain improvement. Also, the patient can have longitudinal care and follow up with other multidisciplinary services such has pain psychology, physical therapy, pain injections, medication management, and continual pain assessments and benchmarking.

1.8 Summary

- A thorough history and physical is essential to establish a working differential diagnosis
- Perform any diagnostic tests needed to confirm a suspected pain etiology
- Assess prior successful and unsuccessful therapies that the patient has tried
- Continue the patients existing home medication regimen
- Institute a multimodal and multidisciplinary treatment plan including anti-inflammatory drugs, steroids, antipsychotic drugs, antiseizure drugs, and pain injections/regional anesthesia
- Consult appropriate external medical services as necessary
- Follow up with the patient as an outpatient to wean the patient from additional opioids that have been prescribed as an inpatient and continue care in a clinic setting that involves a multidisciplinary approach until pain has improved or returned to baseline

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Chapter 2
Patient with a Spinal Cord Stimulator

Jay Karri, Maxwell Lee, Jennifer Sun, Dawood Sayed, and Alaa Abd-Elsayed

2.1 Introduction

Spinal cord stimulation (SCS) is an increasingly used modality for the management of various chronic pain syndromes including, but not limited to complex regional pain syndrome, failed back surgery syndrome, peripheral neuropathic pain, and even refractory angina pectoris [1, 2]. SCS operates by producing electrical impulses along the dorsal columns to preferentially activate A-delta and C fibers, thereby closing the gate for peripheral noxious stimuli to propagate along ascending pain pathways [3, 4]. SCS is particularly promising because it not only delivers significant analgesic benefit, but it does so without producing harmful systemic adverse effects. There also exists data suggesting that SCS can reduce systemic opiate requirements and increase overall functionality.

Providers must be cognizant of SCS-specific procedural complications that may lead to severe and devastating neurological consequences if not identified and appropriately managed [5, 6]. Additionally, there exist many specific inpatient considerations when caring for persons with SCS devices. These considerations need to be carefully and effectively managed to maintain the safety profiles associated with these devices. In order to appreciate how these complications and considerations arise, one must have an understanding of SCS machinery.

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2.2 SCS Device Mechanism

Following a successful SCS trial, a permanent implantation follows wherein a battery-operated and programmable implantable pulse generator (IPG) is surgically placed under the subcutaneous layer of the abdominal wall or back flank [7, 8]. This IPG is intraoperatively connected to the stimulator leads, which are percutaneously introduced into the epidural space under fluoroscopic guidance (Fig 2.1). The level of the electrode lead placement can vary and is largely dependent on the underlying pain etiologies targeted. While mid-thoracic levels, namely T8, are utilized for chronic low back pain conditions, cervical placements have been utilized for chronic upper neck and upper limb pain syndromes. Traditionally, SCS systems delivered tonic stimulus waveforms with good benefit. In recent years, the use of high frequency and burst stimulus waveforms have gained popularity, largely for their capacity to deliver paresthesia-free analgesia with superior benefit in certain contexts [9].

Each component of the SCS machinery is susceptible to damage and/or malfunction and can disrupt analgesic delivery as a whole. Consequently, both IPG and electrode components must be considered in scenarios of suspected SCS compromise.

2.3 Common SCS Complications

2.3.1 Hardware Complications

Hardware complications comprise the most common type of SCS-specific complications that occur. In a retrospective review of 707 patients, Mekhail et al. reported a hardware-related complication rate of 38% in persons with SCS implants [5]. Hardware complications following SCS implantation include electrode lead migration, lead fracture, and battery failure.

2.3.2 Electrode Migration

Out of all hardware complications, electrode migration is the most common. The rates of electrode migration vary among the different studies, ranging from 10.2 to 22.5% [5, 10]. These migrations commonly occur as a result of postural malpositioning or faulty anchoring [11]. When the leads are unable to remain fixed at a given load and spinal posture, notably secondary to a fascial tear or suture failure, electrode migration can result. Thus, proper implantation technique is of the utmost importance. This complication is most commonly observed within 4 weeks of the implantation procedure, after which connective tissue fibrosis fixates the electrode in location. Consequently, during this critical period, patient activity restrictions often include avoidance of vigorous and strenous activity including repetitive bending and twisting.

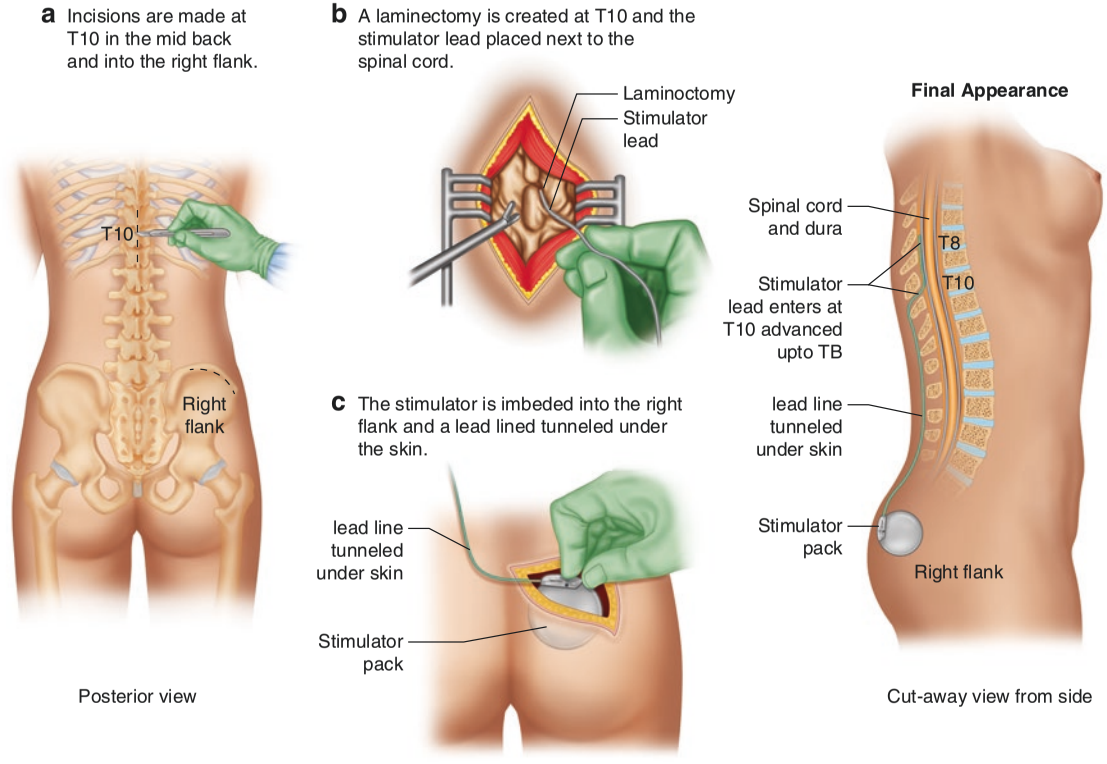

Fig. 2.1 Spinal cord stimulator structure and procedure. (**a**) Incisions are made at T10 in the mid back and into the right flank. (**b**) For surgical placement of stimulator leads, a laminectomy (for paddle lead placement) is created at T10 and the stimulator lead placed overlying the spinal cord doral columns. Percutaneous lead placement does not require laminectomy for placement. (**c**) The implantable pulse generator is imbedded into the right flank and connected to the stimulator leads, which were tunneled under the skin

Common patient presentations that may indicate electrode migration involve new-onset loss of pain control or requisite changes of voltage to achieve the same amount of analgesia. For those using tonic stimulation devices, new regions with paresthesias may also manifest. While reprogramming the implanted device to utilize different lead contacts may be successful in correcting the problem in certain cases, most cases may require a procedure to reposition the lead [10, 11]. Radiographs can confirm the location of electrode migration. In some rare cases, radiographs may not detect a migration, despite symptomatic presentation.

There are a few prevention strategies to lower the rates of complications secondary to lead migration. With the introduction of quadripolar and octapolar electrodes, need for surgical correction has decreased due to the efficacy of higher electrode contacts in reprogramming success [7, 12]. Using paddle-type surgical electrodes may decrease rates of electrode migration compared to percutaneous electrodes. Surgically placed paddle electrodes have two fixed points, whereas PE only has one. Some studies reported that placement of IPG in the abdominal region is preferable to the gluteal region [7, 12].

2.3.3 Lead Fracture

Electrode fracture or breakage is another complication seen in SCS implantation, with one study reporting a 9.1% fracture rate in a study group of 2753 patients and another reporting four cases in a study group of 107 patients [13, 14]. IPG placement into the abdomen has decreased risk of lead fracture compared to gluteal region placement. Weight gain and pregnancy may increase the risk for lead fracture due to increased abdominal circumference [14]. Electrode fractures present with loss of pain relief, and patients may even report burning-type pain [7]. Increased impedance is suspicious for lead fracture, and radiography can often be used as a confirmatory diagnostic tool. Kumar et al. reports that the usual site of fracture involves the deep fascia at the lead entry point into the spinal canal [7].

2.3.4 Battery Failure

The current standard of practice involves using an IPG, which contains a battery, to power the SCS device. Battery life depends extensively on the manufacturer, typically ranging from 4–5 years after which IPG replacement is necessary. A battery failure is defined as requiring a replacement before the expected date, which depends on charge and waveform parameters specific to the patient [14]. This hardware-related complication is rare; in fact, it has not been widely reported in literature. In one 20-year literature review, Cameron reported a battery failure rate in 32 out of 1900 cases, a complication rate of 1.7% [13].

Rechargeable batteries have emerged as a possible solution to premature battery failure, with lifespans of around 9 years [14]. However, they present several issues, including the need for increased patient awareness and compliance, the need for

trained technicians, and the need for daily to weekly recharging, which can serve as an inconvenience to patients.

2.3.5 Device Related Infection

Infection rates across studies in SCS implantation range from 2.5 to 14% [7]. Eldabe et al. reported a range from 4 to 10%, which represent a substantial increase from the 2–5% infection rate observed across all surgeries in the US [15].

The most common site of infection is the IPG pocket site, followed by SCS leads sites and the lumbar incision sites [13–15]. Depending on the severity and spread of infection, complete removal of the system and subsequent treatment with intravenous antibiotics may be necessary. One study reported Staphylococcus species, of which S. epidermidis was the most prevalent, as the most common cause of infection in SCS implantations; Pseudomonas species were isolated in 3% of cases [15]. There have been reports of septic and aseptic meningitis after removal of SCS [14]. Factors that increase the risk of developing infection during the SCS implantation process include diabetes, debility, malnutrition, extremely thin body habitus, obesity, autoimmune disorders, corticosteroid use, decubitus ulcers, pre-existing infections, poor hygiene, urinary or fecal incontinence, and malabsorption syndromes [14].

The most common presenting signs of localized infections involve wound erythema and localized incisional pain [16]. In a study by Bendel et al., in those patients who developed infection, median onset of infection was 27 days (range 2–967) with 62 of 67 infection occurring within the first 365 days; explantation was ultimately required in 77.6% of patients [17]. In Mekhail et al.'s study of 707 patients, 4.5% of patients developed infection, but none had permanent neurological complications or other systemic sequela [5]. Skin erosions can occur, typically as a result from implantations that are too superficial or in patients with thin body habitus or significant weight loss [18].

Most of the time, septic infections developing after SCS implantation require explantation of the device, as antibiotics alone are ineffective [16]. There is no good data on the timing of re-implantation, though recommendations include waiting for control of active infection, confirming the absence of signs of systemic infection, and choosing a different implantation.

Feared, but very rare, infectious complications are meningitis and epidural abscess. These are more commonly seen in intrathecal drug delivery systems, because these systems necessitate refill procedures, which increase the risk for introduction of skin flora into the intrathecal space [15–17].

2.3.6 Neurological Complications

Though rare, neurological complications from SCS implantation can be extremely devastating and life-threatening [15–18]. Consequently, measures to identify and intervene upon suspected scenarios of neurogenic comprise are instrumental to pre-

vent permanent complications. While they can occur following a plethora of etiologies, neurologic compromise—usually to the exiting spinal nerves, nerve roots, or spinal cord—following SCS implantation may be resultant of epidural hematoma formation, spinal cord compression, vascular compromise, or even direct neurotrauma via puncture or crush injury. Regardless of the etiology, concerning symptoms include post-procedural unilateral or bilateral paraparesis, numbness, bowel and/or bladder incontinence, or intractable back pain. After confirming the precise inciting etiology with imaging, prompt neurosurgical evaluation and intervention may be necessary for spinal decompression and/or device explantation.

Less severely, dural puncture is a common complication, with one study reporting post-dural headache in 18% of patients [18, 19]. Risk factors include obesity, spinal stenosis, and epidural scar tissue—as may be present with previous surgery at the site of implantation. It is particularly suspected in cases of notable CSF leakage and is managed with hydration, caffeine, and rest. In cases with spinal headaches refractory to these conservative measures, an epidural blood patch may serve a therapeutic role, but may lead to complications itself [20].

One literature review reported 83 of 44,587 cases (0.19%) with resultant epidural hematoma, and of those 83 cases, only 8 did not recover and were left with a motor deficit [19]. In the same study, 6 out of the 44,857 patients developed autonomic dysfunction and 2 did not fully recover; dural puncture was observed in 21 patients, of which complete recovery was reported in 11 patients.

One other study reported very low rates of severe neurological complications, with 0.5% of patients developing spinal cord injury, 0.5% developing hematomas, though these results may have been confounded by preexisting cervical spondylotic myelopathy or cervical spinal stenosis [21].

2.4 Management of Non-SCS Complications

2.4.1 MRI Considerations

There exist many clinical scenarios where magnetic resonance imaging (MRI) is superior to other imaging modalities and may be necessary to direct appropriate diagnosis and management [22, 23]. Grossly, it is estimated that approximately 82% of persons with implanted SCS systems require an MRI within 5 years of implantation. These estimates are fair and expected given the high prevalence of medical comorbidities in the chronic pain patient population.

Historically, MRI testing was deemed risky in persons with SCS systems. The three principal magnetic fields utilized by MRI are pulsed gradient, static, and radiofrequency fields, and each convey various risks on SCS systems. Notable risks are largely divided into magnetism associated device failure and/or focal tissue damage.

Device failure with MRI ranges from changes in stimulation program, lead impedance, battery exhaustion, and implantable pulse generator malfunction. The pulsed gradient fields are thought to be the primary drivers of magnetism-induced

voltage and current modulation. Collectively, all of these complications (grossly estimated to be ~18.5% in prevalence) can result in suboptimal analgesic benefit and thus post-MRI SCS device interrogation and subjective pain assessment can be useful to screen for such complications [22]. Static magnetic fields confer ferromagnetic attraction to cause shifting of metal containing implant devices. While this risk can theoretically serve to cause shifting and migration of SCS leads, no such reports have been reported in the literature. Focal tissue damage (grossly estimated to be 11.1% prevalent) occurs secondary to magnetism induced heating of SCS leads, by way of radiofrequency magnetism fields. There have also been reports of painful dysesthesias with MRIs [22, 23].

With recent technological advances, MRI scans of the head and peripheral extremities have been found to be safe to obtain. Additionally, implementation of specific MRI protocols has been shown to be safely utilized for imaging other parts of the body with only minor and non-threatening complications reported. While SCS-specific MRI protocols can be utilized, patient positioning that serves to maximize distance of the imaging coils to the SCS leads can also help further mitigate associated risks.

Even more recently, MRI scans of the thoracic, abdominal, and pelvic compartments have been made possible by recent FDA-approved SCS technologies. Rubino et al. provide a extensive overview of various SCS systems from varying device manufacturers and outline which body regions and MRI settings can be utilized [23]. Overall, SCS device representatives can and should be consulted to help provide guidance regarding MRI compatibility, especially in persons with older systems. This consultation and appropriate discussion with the overseeing radiologist and technicians can help mitigate MRI-associated complications and risks.

2.4.2 Cardiac Implantable Electronic Devices

With the overall increase in prevalence of heart disease in the United States, so too has there been an overall increase in the utilization of Cardiac Implantable Electronic Devices (CIED) for the management of arrhythmias [24]. These devices commonly include permanent pacemakers (PPM) and implantable cardiac defibrillators (ICD),which help control sinus pacing of the heart and treat life threatening arrhythmias, respectively. Both devices operate by detecting cardiac rate and rhythm and dispensing electrical energy to rectify arrhythmias. Consequently, there exist potential hazards of SCS systems producing electrical interferences that may obviate CIED function. While some remote reports have shown SCS systems nullifying CIED function, more recent evidence suggests that concomitant SCS and CIED utilization can occur with the necessary multidisciplinary collaboration, controlled interference testing, and device-specific considerations [25]. The most recent Spine Intervention Society investigation into the matter has resulted in a statement deeming SCS as a safe treatment in persons with a CIED should appropriate collaboration with the involved cardiologist/electrophysiologist occur [26].

Given that CIED placement is a life saving measure, it's functionality should take precedence over that of an SCS when both technologies are being considered. Therefore, appropriate cardiac risk stratification and collaboration with cardiologists/electrophysiologists are warranted when patients are deemed appropriate for both technologies. This will allow for both parties to make device specific considerations (CIED lead polarity and system programmability; SCS frequency systems and system programmability) in accordance with device manufacturers for both products. Additionally, this will also allow for the involved cardiologists/electrophysiologists to carefully monitor the patient following dual device utilization for the development of cardiac related adverse effects. Patients should always be counseled of the risks associated with dual SCS and CIED implantation and be prepared for possible SCS explanation should irreparable interference patterns be identified.

Torre-Amione et al. published a well-designed, randomized, placebo-controlled, crossover study investigating ICD efficacy in a cohort of 9 patients with advanced heart failure who received SCS implantation and subsequent null and active SCS treatments with paresthesia production [27]. Active SCS treatment was not found to cause any interference preventing the ICD from receiving, analyzing, or dispensing corrective electric therapy. This interference testing involved an elegant intraoperative algorithm for the measurement of ICD function following SCS implantation.

First, SCS amplitude was reduced to a 90% subperceptible level [28]. Thereafter, ICD intracardiac electrocardiograms were analyzed for any evidence of SCS induced myopotentials. If any SCS activity was identified in this intrinsic electrocardiogram measurement, SCS reprogramming was warranted. Subsequently, ventricular fibrillation was induced, and ICD response was measured by time to arrhythmia detection and diagnosis along with number and strength of shocks dispensed. This interference testing approach allows not only for intraoperative SCS reprogramming to avoid gross SCS myopotential detection, but also to measure ICD function in context of SCS treatment. Such testing allows for abortion of SCS system permanent implantation in scenarios where ICD function may be compromised. Given that recently developed SCS systems, including those with burst and high frequency waveforms are paresthesia-free devices, novel protocols for concomitant CIED candicacy are necessary.

2.4.3 Perioperative and Acute Pain Considerations

There are many perioperative considerations for persons with SCS systems undergoing surgical procedures [29]. In the setting of neuraxial anesthesia, it is instrumental that needle placement does not compromise the SCS electrodes. Compromise of SCS electrodes can result in lead fracture at the severe spectrum and migration on the milder spectrum. Electrode migration can result in loss of analgesic benefit and require procedural driven electrode repositioning. Thus, reviewing prior imaging to identify SCS placement and electrode placement may help in preparation of

planning for epidural access. Even if epidural access is obtained, others have suggested that neuraxial analgesia may be ineffective this patients with SCS systems given the likelihood of epidural fibrosis [30, 31].

If the implanted SCS electrodes cannot be avoided, general anesthesia could be considered if reasonable and appropriate. Lastly, topical antiseptic use is of high importance to prevent procedural infections. Microbial prophylaxis is particularly important for SCS device preservation, as central nervous system infections may lead to device explantation [31].

Acute pain syndromes, such as post-surgical pain, are often self-limiting conditions that resolve across a short time span of days to weeks without significant chronic sequelae. Current convention for managing acute pain conditions includes pharmacological management, including opiates, and anesthetic peripheral nerve blocks, as common with major joint arthroplasties [31–33]. Use of SCS for the treatment of acute pain conditions, however, is not indicated and lacks significant evidence.

Of note, Lawson et al. report a case of a patient with severe acute-on-chronic pain following a cervical decompression surgery for degenerative cervical myelopathy secondary to cervical spinal stenosis [34]. The reported pain was so intractable that it was controlled only with escalation to intravenous ketamine and midazolam. Following implantation of a cervical SCS system for management of acute post-operative pain, the patient experienced significant relief.

Further reports and stronger evidence for SCS in acute pain conditions are largely lacking. Therefore, management of acute post-operative pain in persons with pre-surgical SCS implants should be largely similar to that in persons without SCS implants. It is important, however, to direct acute pain treatments towards the treatment of the acute pain condition only. This scope of treatment prevents patients from exposure to chronic opiates and overall pharmacotherapy escalation for the treatment of chronic pain—this strategy can help mitigate inappropriate opiate exposure and its resultant complications.

Likewise, it should be noted that patients with chronic pain treated with SCS systems may have some degree of baseline pain. Therefore, achieving complete analgesia may be unlikely and should nonetheless not be sought after in the setting of acute pain treatment. Similarly, escalation of chronic pain pharmacotherapy for chronic pain indications should be postponed until the acute pain condition resolves.

2.4.4 Pain Management for Other Reasons

Patients with an implaned SCS may show up to the emergency room for pain related to other conditions e.g. uncontrolled low back pain, rib fractures and other conditions. It is very important to know the device model and manufacturer to understand the locations of the leads and battery, MRI compatibility. Pain in those conditions should be treated using routine modalities as regional blocks, non-pharmacological and pharmacological modalities.

2.5 Summary

- SCS has extensive supportive evidence for treating numerous chronic pain conditions including failed back surgery syndrome, complex regional pain syndrome, and refractory angina pectoris.
- Complications with SCS, while rare, can result in devastating neurological outcomes, including paraplegia, and thus early investigation and management is necessary when neurologic compromise is suspected.
- The most common hardware complication is electrode lead migration, which can result in loss of paresthetic or analgesic coverage and, possibly, efficacy.
- MRI compatibility, while increasingly common with newer SCS systems, should be investigated and discussed with the patient, device representative, and radiologist.
- While CIED placement does not contraindicate the concomitant use of SCS systems, careful diagnostic investigations must occur to ensure that both the CIED and SCS are appropriately functional together.
- *In persons with SCS systems, treatment of acute pain conditions should not be compromised. Management of chronic pain should occur following resolution of the acute pain condition such that unnecessary opiate escalation does not occur.*

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Chapter 3
Patient with an Intrathecal Pain Pump

Jay Karri, Maxwell Lee, and Alaa Abd-Elsayed

3.1 Introduction

Intrathecal drug delivery systems (IDDS) are increasingly used modalities for the management of various chronic pain syndromes including cancer pain, CRPS, and failed back surgery as well as non-pain syndromes such as uncontrolled quadriparetic or paraparetic spasticity [1, 2]. Given that intrathecal medications are largely confined to the epidural space, microgram medication dosages are able to be utilized with a great degree of efficacy. Thus, IDDS also allow for the weaning and possible discontinuation of systemic pain and spasticity medications, which are associated with various systemic adverse effects.

Many high quality research studies and consensus guidelines have helped dictate which intrathecal medications are effective for varying indications [2–6]. Currently, the only FDA approved intrathecal medications include morphine and ziconotide for the management of chronic pain and intrathecal baclofen for the management of spasticity. However, many other medications including local anesthetics (largely ropivacaine, bupivacaine, levobupivacaine), other opiates (hydromorphone, fentanyl), and clonidine are commonly used, sometimes in combination, to manage chronic pain (Table 3.1).

Persons with IDDS can pose various considerations in the inpatient setting that must be carefully addressed. These questions may be related to potential post-procedural complications or other IDDS specific considerations and need to be

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Table 3.1 Intrathecal medications, mechanisms, and maximum dosages

Medication	Mechanism	Maximum concentration (μg/mL)
Ziconotide	N-type voltage-gated calcium channel blocker	100
Morphine	Opioid agonist	20
Hydromorphone	Opioid agonist	15
Fentanyl	Opioid agonist	10
Sufentanyl	Opioid agonist	5
Bupivacaine	Sodium channel blocker	30
Clonidine	Adrenergic alpha2-Agonist	1000
Baclofen	$GABA_b$ channel agonist	2000

Largely adapted from recent PACC recommendations [3]

carefully and effectively addressed to maintain appropriate safety profiles. In order to appreciate how these complications and considerations arise, one must have a well-versed understanding of IDDS machinery [7].

3.2 IDDS Mechanisms (Fig. 3.1)

Following a successful intrathecal drug trial, an IDDS implantation occurs wherein an implantable pump is surgically placed under the subcutaneous layer of the abdominal wall or back flank [2, 8]. This pump is intraoperatively connected to a catheter which terminates in the epidural space. The catheter tip positioning can vary extensively depending on the pathology present. While a vast majority of catheter tips are positioned in the low-thoracic and lumbar levels for chronic pain syndromes, cervical catheter placement can occur in certain scenarios including quadriparetic spasticity. The multiple components of this machinery are each susceptible to mechanical failure and may disrupt the integrity of the drug delivery system as a whole.

Persons with IDDS placement require pump refills at a frequency largely determined by the concentration of the intrathecal medication and rate of drug infusion. With each pump refill, the IDDS program calculates the latest date for the subsequent pump refill. Should the pump not be refilled prior to this date, the IDDS emits a high frequency "non critical alarm"—usually single toned depending on the model and manufacturer of the system—to indicate that the reservoir volume requires repletion [9]. The threshold of the low reservoir volume, although conventionally placed at 2 mL, can be modified. Should the "non critical alarm" fail to be addressed, the IDDS system will eventually emit a high frequency "critical alarm"—usually dual toned depending on the model and manufacturer of the system—to indicate that the reservoir volume is near or fully depleted and needs to be urgently addressed.

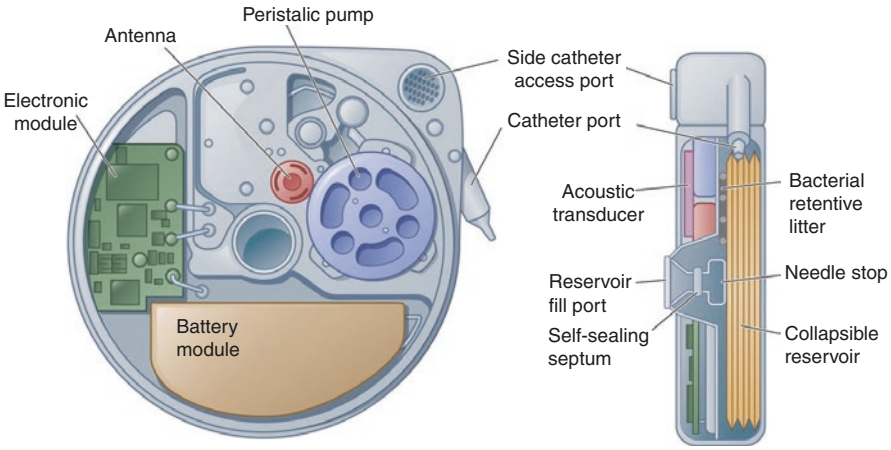

Fig. 3.1 Intrathecal pump structure

Table 3.2 IDDS devices and their varying considerations

Device	Mechanism	Infusion strategies	MRI considerations
Synchromed II by Medtronic™ FDA approved for Pain and Spasticity	Peristaltic pump	"Patient therapy manager" allows for patient controlled bolus delivery to augment continuous infusion	No need to remove medication from reservoir prior to MRI study
Prometra by Flowonix™ FDA approved for Pain	Valve-gated system	Continuous infusion only	Requires removal of medication from reservoir before MRI study

3.2.1 Different IDDS Devices

There exist only two FDA approved IDDS devices in the United States market: the Synchromed II by Medtronic™ and the Prometra by Flowonix™ [10–12]. These two devices vary extensively in regard to mechanism, approved indications, infusion strategies, and even magnetic resonance imaging (MRI) compatibility (Table 3.2).

3.3 Common IDDS Complications

While the overall risk of major complications related to IDDS placement is low, persons with IDDS are susceptible to a host of complications that can occur at any time after pump implantation [1, 8, 9, 13]. These complications vary in etiology and

can lead to severe morbidity or mortality. Therefore, providers must always maintain a healthy index of suspicion for these complications in order to provide early and appropriate management.

3.3.1 Procedural Complications

Despite measures to mitigate risks of neurological injury—from pre-procedural anticoagulation weaning to using fluoroscopic guidance to confirm catheter placement in the epidural space—neurological compromise to the nerve roots or spinal cord itself can occur either directly via needle or device trauma or secondarily via hematoma formation [2, 13, 14]. Consequently, providers should monitor patients in the post-procedural setting for alarm signs and symptoms of neurological compromise which can include but are not limited to unilateral or bilateral paraparesis and intractable back and/or leg pain. Persons with concern for neurological compromise warrant emergent computerized tomography (CT) imaging of the spine to identify possible etiologies of neurotrauma and determine if emergent neurosurgical intervention is needed to prevent devastating neurological outcomes. MRI may be possible in the correct context, with compatible devices, as delineated in the section below.

Less severely, post-dural puncture headaches are more common and can occur with increased cerebrospinal fluid (CSF) leakage [8]. Persons with prior spinal surgeries are thought to have more epidural scar tissue and thus a greater risk for increased CSF leakage. Aside from a post-dural puncture headache, CSF leakage can also cause subcutaneous swelling, impaired wound healing, hygromas, and infections, all of which may warrant surgical intervention. Additionally, wound seromas may form around the surgical site. Though mostly self-limiting and spontaneously resolving, these seromas may require systemic antibiotics and/or drainage [15].

As with any procedure, there is an inherent risk of infection. Despite the use of peri-procedural prophylactic antibiotics and irrigation of incision sites with antibiotics, and even placement of vancomycin power in the IDDS pump pocket, peri-procedural infections can occur and lead to meningitis, epidural abscesses, pump pocket infections, and catheter tip infections [1, 8, 16]. Most infectious complications are thought to occur in the first 3 months following IDDS implantation. Therefore, careful, frequent, and close monitoring for signs and symptoms of infection around the implant site is necessary during this period. While superficial infections may be managed in the ambulatory setting, deeper infections and/or those which cause sepsis may require device explantation, especially with the development of intrathecal and epidural infections. Additionally, early CSF cultures (includ-

ing a set from the catheter access port) and spinal imaging should be collected to characterize the infectious etiology. Abscesses or loculated fluid collections may necessitate operative interventions.

Clinically significant bleeding is also a possible surgical complication. The causes are manifold, including but not limited to, preoperative anticoagulation, coagulopathy, and vascular injury. While the most feared bleeding complications cause neurological compromise, as aforementioned epidural or perineural hematomas, superficial hematomas and post-operative bleeding can also occur [2]. Most of the time, scant or superficial bleeding is self-limited and is likely to resolve with compression wound dressings and adherence to abdominal binder placement.

3.3.2 Mechanical Complications

The IDDS is comprised of a host of mechanical components, each of which is susceptible to failure and dysregulated intrathecal drug delivery. While underdosing and resultant withdrawal is common in such occurrences, overdosing may also be possible and thus patients may also present with resultant drug toxicity [15–17].

Within the intrathecal pump, a mechanical failure secondary to loss of pump propellant, gear shaft wear, and motor stalls are all possible [16, 17]. These complications can occur by virtue of battery expiration or failure, or even following MRI testing. Aside from the pump itself, disruptions to catheter integrity are far more likely. Fluckiger et al. in a large scale review of a single center experience with IDDS across a 12 year span found that 65% of all IDDS complications were catheter related while 35% were pump related [16]. Catheter disconnection may be secondary to kinking or fracture, while catheter obstruction may also be possible via catheter tip granuloma (CTG) formation, catheter tip fibroma, or fibrous sheath obstruction [8, 15, 17]. Despite the precise mechanism, all of these etiologies can interfere with drug delivery and result in decreased analgesia, worsened chronic pain, and withdrawal symptoms [17]. However, overdosing may also occur and drug toxicity should not be excluded.

The approach to investigating IDDS mechanical complications is suggested to start with identifying catheter continuity/discontinuity. Miracle et al., thus suggest plain radiography and device interrogation to be first line diagnostic measures [18]. Should no overt catheter discontinuity be identified by these measures, contrast studies should be pursued to identify presence and location of catheter compromise. First, CSF aspiration should be attempted from the catheter access port to determine if the catheter is patent [18, 19]. If CSF aspiration is successful, contrast agent may be injected into the catheter access port and dye flow patterns can be analyzed on fluoroscopy, however, CT imaging may be more sensitive.

3.3.3 Pharmacologic/Refill Complications

Generally very rare, CTGs are aseptic inflammatory masses that form secondarily to an unclear and incompletely characterized pathophysiology. Nonetheless, CTGs disrupt intrathecal medication delivery and affected patients suffer from severe pain refractory adjustments in intrathecal drug delivery. If large enough, CTGs can produce a mass effect by impinging upon exiting spinal nerves or the spinal cord itself to cause radicular or myelopathic symptoms, respectively [15, 19].

Kratzch et al. and others previously identified catheter position, low CSF volume, medication concentrations, and intrathecal contrast agents as common risk factors for CTG development [20]. Namely, persons with catheter tip placement in the middle thoracic levels and those using high morphine dosages were particularly shown to be more susceptible for CTG formation. Intrathecal sufentanil, baclofen, and clonidine may also be implicated [3, 15, 17]. It should similarly be noted that ziconotide and fentanyl were not found to have a correlation to CTG formation. Furthermore, younger patients and those with chronic nonmalignant pain are more at risk than their older, malignant pain counterparts [21]. The onset of granuloma formation is typically several months after implantation, with one study showing an increasing risk with each year the implant remains in a patient, beginning at 0.04% after 1 year and 1.15% after 6 years [22].

The presence or absence of neurologic symptoms determines subsequent management in these cases. If positive for neurogenic compromise, removal of the device and decompression is recommended by a surgical laminectomy; if negative, weaning the concentrations of the aforementioned implicated medications or changing intrathecal therapy to the lesser implicated fentanyl or ziconotide may be considered [21, 22].

Direct drug toxicities are typically preventable and result from hypersensitivity or allergic reactions, which can be avoided by slow titration. However, complications can be life-threatening, so careful administration must be undertaken. These include medication errors with incorrect doses or concentrations, reprogramming errors, or administration of medication into the pump pocket [21]. In general, adverse reactions to intrathecal medications include nausea, vomiting, constipation, respiratory depression, and headache, to name a few.

However, drug specific adverse effects should be particularly considered. Intrathecal ziconotide may result in dizziness, nausea, vomiting, urinary retention, ataxia, nystagmus, confusion, or the rarely seen psychosis, suicide, and rhabdomyolysis [21]. Neuropsychiatric adverse effects with intrathecal ziconotide are particularly distressing and necessitate discontinuation of ziconotide treatment. Intrathecal clonidine also has side effects, including hypotension, bradycardia, and sedation [21]. Intrathecal opiates confer side effects that are mediated by opiate receptors. Largely, these side effects include nausea, vomiting, constipation, urinary retention with rare occurrences of respiratory depression and hyperalgesia [23]. These side effects can be corrected with naloxone administration and warrant dose adjustments to prevent severe complications [23].

Intrathecal baclofen withdrawal is especially alarming given that it can lead to mortality if not addressed in a timely fashion. Patients undergoing drug withdrawal exhibit symptoms of fatigue, pruritis, irritability, worsened spasticity, and paresthesias [21]. Other more alarming symptoms include blood pressure lability, seizures, and delirium [24]. To mitigate lethal risks of baclofen withdrawal, systemic baclofen or diazepam are often utilized until effective intrathecal baclofen therapy can be restarted [21]. However, intrathecal baclofen is preferred, even as a bolus, due to slower onset of action, time to peak effect, poor absorption, and decreased CSF concentrations with enteral medications [24]. Benzodiazepines (such as lorazepam, diazepam, and midazolam), propofol, cyproheptadine, dantrolene, and tizanidine have also been shown to be effective adjuvant therapy in the setting of baclofen withdrawal.

3.4 Management of other IDDS-associated considerations

3.4.1 MRI Considerations

As conventional, all metallic device implants should undergo screening consideration before an MRI can be considered [25, 26]. New MRI compatible technologies and innovative protocols have allowed persons with IDDS systems to get MRI studies. However, careful consideration and approaches must be utilized given food and drug administration (FDA) reports of serious adverse events and death in persons with IDDS undergoing MRI [25]. These complications were all found to be resultant of aberrant medication dosing and/or hardware function. If the utility of an MRI study in the context of such risks is deemed necessary, the FDA recommends a multidisciplinary collaborative effort for appropriate risk mitigation.

All IDDS patients are provided with an implant card that denotes important system variables including MRI compatibility. Additionally, representatives from the device manufacturer should be notified about a tentative MRI study so that device safety can be cross referenced and ensured. Notably, many devices do not provide comprehensive and overarching MRI compatibility parameters. Depending on the IDDS model, MRI compatibility may be restricted to certain body regions (head or extremity imaging) or strength (limited to 1.5 T field). These conditional parameters should be made accessible to the patient, ordering providers, and radiologist coordinating the study. Of note, De Andres et al. report successful utilization of a conservative MRI protocol (1.5 T and <0.9 W/kg) across multiple IDDS models without any technical or medical complications [25–27].

As aforementioned, aberrant medication dosing can occur following an MRI study. Therefore, pre- and post-MRI IDDS interrogation is instrumental to identify any potential complications and ensure proper functionality. Additionally, measures to monitor and rectify these complications should be prepared to prevent possible lethal sequela of medication withdrawal or overdose. Hardware malfunction of

IDDS following MRI studies may also be possible, by way of motor or pump stalls, and lead to inappropriate medication underdosing or overdosing. In such scenarios, IDDS failure may be permanent and explanation and replacement may be likely necessary. Once again, appropriate medication weaning and/or systemic adjunct medications will be necessary if IDDS failure were to have occured.

3.4.2 Hyperbaric Oxygen Therapy

The efficacy of hyperbaric oxygen therapy (HOT) has been readily demonstrated across numerous contexts including carbon monoxide poisoning and recalcitrant wounds secondary to hypoxia [27–29]. While the use of HOT in patients with IDDS has been little investigated, overall theoretical risks and case reports suggest that HOT may confer IDDS malfunction. Thus, careful consideration of this adverse risk profile is necessary in the management of persons with IDDS being considered for HOT.

HOT induced risks are thought to include (1) explosion secondary to undue friction within pump system, (2) battery leakage, (3) collapse or disruption of internal machinery, and (4) air entry into pump reservoir or catheter. Akman et al. also provide a report of HOT causing retrograde cerebrospinal fluid leakage into the infusion reservoir secondary to elevated intraspinal pressures during HOT [27]. Each of these complications can cause direct patient harm primarily or secondarily via aberrant medication dosing. Prophylactic measures to ameliorate these complications include measures to monitor for and rectify medication underdosing or overdosing as could occur with pump malfunction. Additionally, IDDS interrogation pre- and post-HOT may also be helpful to identify aberrant dosing patterns and possible medication leakage.

Notably, Sanchez-Guijo et al. previously published an interesting case report of pump failure in a hyperbaric environment secondary to pump stalling with HOT at a pressure of 2 absolute atmospheres (ATA) [28]. Interestingly, they also subjected different pump devices to HOT and found that pump stalling occurred at different ATA limits—ranging from 2 to 3.4 ATA. It should be noted that if appropriate considerations are taken, HOT can be a promising therapy in vulnerable populations—notable persons with severe spasticity and intrathecal baclofen pumps—who suffer from chronic pressure wounds. Barket et al. also published findings showing efficacy of HOT in preventing device explanation in persons with neuromodulation devices associated with hardware infections [29]. While a majority of the study included persons with electrical stimulation systems, two persons with IDDS were also included.

3.4.3 Perioperative Considerations and Acute Pain Management

There exist many anesthesia considerations to be accounted in patients with IDDS undergoing surgical procedures. In the setting of neuraxial anesthesia, it is instrumental that needle placement does not compromise the IDDS catheter [30]. Thus,

reviewing prior imaging to identify IDDS placement and catheter route is pertinent along with the use of ultrasound or fluoroscopic guidance to gain successful epidural access. If the implanted catheter or IDDS device cannot be avoided, general anesthesia could be considered, if reasonable and appropriate. Lastly, topical antiseptic use is of high importance to prevent procedural infections. Microbial prophylaxis is particularly important for IDDS device preservation as central nervous system infections may lead to device explantation.

An important preoperative consideration is whether to adjust the intrathecal infusion rate. It is advisable to proceed with caution in decreasing or increasing the rate. Increasing the rate for greater analgesia may result in respiratory depression or excessive sedation; decreasing the rate abruptly, especially of baclofen and clonidine, may result in life-threatening withdrawal and rebound hypertension [31]. While managing intraoperative pain control, the use of non-opiate medications should be optimized [32]. Judicious use of opiates is important to mitigate risks of respiratory depression especially in persons with intrathecal opiate or baclofen medications. The administration of opioids for patients receiving intrathecal baclofen may result in a synergistic effect, and because there is currently no available conversion of intrathecal dosing to intravenous dosing, special care must be taken to avoid overdose [30]. Therefore, the use of non-steroidal anti-inflammatories and acetaminophen should be considered and optimized. Additionally, ketamine infusions are gaining popularity given favorable adverse effect profiles while demonstrating good capacity for analgesic benefit; ketamine boluses may also be used for effective intraoperative analgesia in appropriate patients [33].

Acute pain conditions, such as post-operative pain, are often self-resolving syndromes without chronic sequela. Given that many patients with IDDS may have ongoing intrathecal opiate therapy, careful considerations must be given towards the use/dose of systemic opiates which may serve to amplify opiate associated adverse effects [30, 32, 33]. Consequently, measures to minimize systemic opiate usage and dose should be undertaken. Such measures include increased utilization of non-opiate medications (acetaminophen, non-steroidal anti-inflammatories, and non-opiate narcotics such as tramadol), non-pharmacologic modalities, and even regional nerve blocks with local anesthetics which are increasingly proven efficacious for various post-pain conditions including those associated with large joint arthroplasties.

If the above conservative measures are sub-optimal in delivering necessary analgesic benefit, opiate delivery for acute pain can be considered. Opiate therapy can be delivered either systemically or intrathecally but requires care and caution to avoid adverse effects, particularly respiratory depression in the post-surgical context. Short-acting opiate formulations are considered far preferable to long-acting agents. Depending on the type of IDDS in place, modifying bolus medication delivery may be considered until the acute pain condition can resolve. A temporary increase in basal intrathecal opiate dosages can be considered, but should be reserved for ongoing management of chronic pain.

In summation, opiate supplementation should be reserved for when other modes of management fail. However, given that under treated or ineffectively treated acute

pain can worsen underlying chronic pain and prevent post-operative function and rehabilitation, judicious opiate use rather than altogether avoidance is appropriate.

Lastly, it should be noted that patients with chronic pain treated with IDDS have a degree of baseline pain. Therefore, management of acute pain conditions in this population should be directed towards the acute on chronic pain presentation given that complete analgesia may not be realistic. Similarly, management of the chronic pain should follow the resolution of the acute pain presentation so that a clear and appropriate escalation of chronic pain pharmacotherapy can occur.

3.4.4 Pain Management in the Inpatient Setting

When a patient with intrathecal pump shows up to the hospital for other painful conditions. It is very important to know the pump and catheter location, manufaturer, medication in the pump and infusion rate. Management of pain should be done using a multidisciplinary approach avoiding opioids if possible. Oral opioids in addition to intrathecal opioids can lead to overdosing, sedation and respiratory depression. Providers should use other modaities as tricyclic antidepressants, antiseizure medications, regional blocks and Acetaminophen. Programming of the pump can be done increase the infusion rate of intrathecal opioids which can provide more pain relief.

3.5 Summary

- IDDS is a readily used modality for treating various chronic pain conditions, largely including cancer pain, CRPS, and failed back surgery syndrome, and non-pain conditions such as severe spasticity.
- The only FDA approved intrathecal medications include morphine and ziconotide for pain, and baclofen for spasticity.
- IDDS related complications are procedural, device-related, and medication associated in nature.
- Procedural complications can involve neurologic compromise and thus early investigation and management are often necessary to prevent devastating neurologic outcomes.
- Device compromise can occur with malfunction of the pump or the catheter. Isolating the deficit in the circuitry can involve device interrogation, plain radiography, and contrast studies via fluoroscopy or CT guidance.
- Medication related complications are largely secondary to human error with pump medication refills. Careful management and oversight are needed as intrathecal baclofen withdrawal can cause death if uncorrected.
- A multidisciplinary approach with the patient, device manufacturer, and radiologist can help ensure MRI studies are safely conducted in persons with IDDS.
- HOT may be safe and appropriate in persons with IDDS, but careful monitoring is nonetheless necessary.

- Persons with IDDS who experience acute pain conditions, non-opiate medications and non-pharmacological pain modalities should be optimized. In severe cases, bolus intrathecal medications can be considered. The management of chronic pain with IDDS should largely be delayed until the acute pain condition resolves.

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Chapter 4
Patient with a Deep Brain Stimulator

Rudy Garza III, Cory Jones, and Maxim S. Eckmann

4.1 Introduction, a Brief History of Deep Brain Stimulation

Electrotherapy for pain has been used since the first century, although the current methods are much more sophisticated than the crude use of the Numbfish. The evolution of using electricity from a fish to treat pathologies has now evolved to a neuro-modulating implantable device that can diminish symptoms of refractory movement disorders, such as Parkinson's disease, which was treated primarily by surgical interventions prior to the 1970s. Surgical interventions carried high complication risk including hemiparesis as lesions were created along the pyramidal or descending tracts. Following the advent of levodopa, a prodrug that is converted to dopamine by DOPA decarboxylase, pharmacologic management became the mainstay treatment option. However, it also became clear that patients on levodopa and other antiparkinsonian drugs often develop significant drug-induced complications, such as involuntary muscle movements, hallucinations, and psychosis. In 1952, an inadvertent ligation of the anterior choroidal artery introduced insight into the basal ganglia, thalamus and how this circuitry can be used to treat movement disorders. Eventually, stereotactic interventions to create lesions in these areas were developed, but still would result in undesirable sequelae such as problems with speech and cognition [1, 2]. This discovery, however, demonstrated that modulation in certain areas of the brain can have profound effects on patients' symptoms. A few years after this discovery, the work of Heath and Mickle showed that stimulation of the septum resulted in successful treatment of intractable pain. This discovery led to the birth of intracranial stimulation for treatment of pain syndromes. Eventually, other sites were studied and include the internal capsule (IC), the ventral posterolateral nucleus (VPLP) and the ventral posteromedial nucleus (VPM) of the sensory

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thalamus (STH), the centro-median parafasicular region (CM-Pf) of the thalamus, the periaqueductal/paraventricular gray (PAG/PVG), the posterior hypothalamus (PH), the motor cortex, the nucleus accumbens (NAcc), and the anterior cingulate cortex (ACC) [3]. The three regions emphasized in chronic pain are the PAG/PVG (stimulation is thought to treat nociceptive pain), the VPL/VPM in the thalamus (neuropathic pain), and the ACC (affective pain) [4].

Although Deep Brain Stimulation (DBS) can be used for the treatment of chronic pain, it is currently considered off label use. Because of this limitation, the total number of patients who have had DBS surgery for intractable pain is quite low, although the exact number is not known. In 2005, a meta-analysis reported roughly 400 patients with DBS implanted for the indication of chronic pain. In the last decade only three studies have been performed, the last of which only studied 10 patients [5]. Due to the lack of power driving the data, no concrete conclusions can be reached, and clinical judgement should be used to determine the best approach to each individual patient. Although there are general guidelines available for managing patient with DBS, there are no clear, validated, or established programming protocols for the device. While the literature currently lacks definitive evidence for specific uses of DBS in chronic pain, there are a few types of pain conditions that can potentially be treated by DBS: nociceptive pain, neuropathic pain, and potentially affective pain [5].

4.2 Pathophysiology

Despite long-term and widespread use of deep brain stimulation (DBS) for neurological, movement, and pain conditions, the underlying mechanisms of action in the treatment of pain has not been fully understood. DBS can be effective if and when placed in well-selected patients with refractory neuropathic or nociceptive pain. Although the treatment effect is more pronounced in patients with nociceptive pain, there is growing evidence of the benefits involving deafferentation pain conditions. These conditions include failed back surgery syndrome (FBSS), phantom limb pain, peripheral neuropathic pain, and cephalgias, with cluster headaches specifically showing promising results. The success of DBS is dependent on many factors including selection of appropriate patients, accurate placement of DBS lead, and a thorough programming process to identify the optimal stimulation parameters [6]. DBS came in favor due to it being reversible, adaptive, adjustable and less invasive in comparison to previous surgical options. It was initially approved by the Food and Drug Administration (FDA) for pain following a multicenter study, but this approval was ultimately retracted with the FDA requesting further trials to determine efficacy and safety [7].

Much of our current understanding of DBS is based on studies investigating Parkinson's disease. Growing evidence suggests that DBS acts through multimodal mechanisms that are not limited to inhibition or excitation of the basal ganglia or

other specific targets. To further complicate the matter, DBS elicits variable responses over time suggestive of a more complex mechanism of action. Initial theories attributed the pathophysiology to alterations in the rate of neuronal firing in the basal ganglia. Therefore, if targeted, a therapeutic effect may be achieved if stimulation disrupts the abnormal synchronization of the basal ganglia's circuitry, allowing normalization and restoration of 'functionality' rather than actually repairing the pathological basal ganglia system [8].

This theory may be true for movement disorders, but for pain conditions other targeted areas were investigated and showed improved results. Meta-analysis of DBS for chronic pain demonstrated long-term pain alleviation when stimulation is targeted at the periaqueductal gray matter (PAG)/ (PVG) periventricular gray matter or the PVG/PAG plus sensory thalamus/internal capsule [9]. DBS of the PAG is thought to enhance endogenous opioid release and to exert ascending modulation of the ventral posterior nucleus of the thalamus [10], whereas DBS of the PVG is thought to modulate autonomic function [11] by engaging passive coping mechanisms alongside increased vagal output [12]. Levy et al. performed a review of the literature and found a range of success from 47 to 60% with up to 80 months follow-up in the use of DBS for chronic pain [13]. The literature continues to evolve when looking at DBS as an intervention for these indications with Parmar et al. describing overall efficacy for refractory pain in both nociceptive pain (61%) and phantom limb pain (71%) [14] Multicenter controlled trials are still lacking, and the present research has demonstrated variable results. A review of the literature, however, does demonstrate that it carries favorable results for various indications in select patient that have not been successful such as medications, conservative measures, and extracranial procedures (Fig. 4.1).

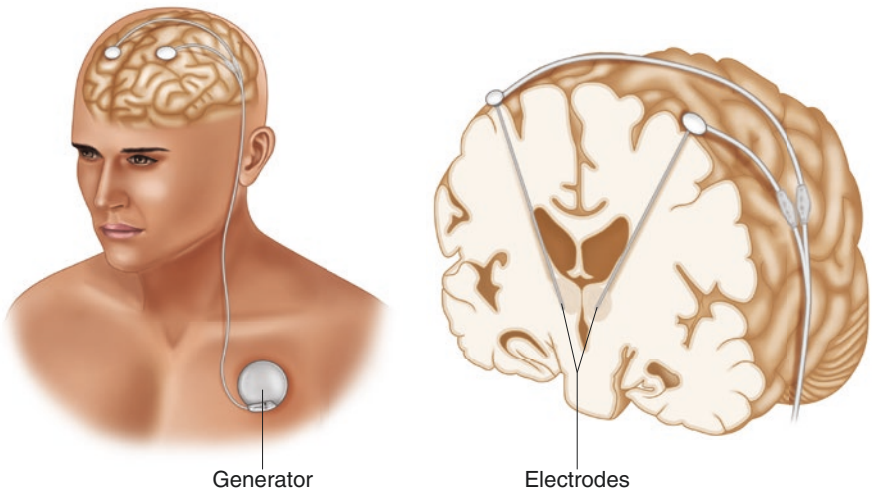

Fig. 4.1 Components of the deep brain stimulator

4.3 Diagnosis

The etiology and treatment of pain exacerbation in a patient with a DBS admitted to the hospital can be challenging for multiple reasons. Patient with DBS placed for intractable pain usually have failed all other treatment modalities, so differentiating between chronic or acute pain may guide your decision algorithm. Also, given the lack of training or experience in managing DBS, most practitioners may find it difficult to discern whether or not their pain stems from a malfunction of the DBS, or another source.

The most important initial step in the evaluation of the patient is the initial history and physical examination. When consulted on a patient with a DBS, you must first identify the indication for implantation as this can guide you on your treatment options. The majority of devices were implanted for dystonia or for a type of movement disorder. More than half of patients with movement disorders will experience some form of physical discomfort or chronic pain symptoms frequently caused by poor posture, arthritis and constant involuntary muscle movement. In some cases, chronic pain may be due to nerve damage, a direct consequence spinal degeneration or changes in the spinal curvature. Optimal management of comorbidities and their associated medications (e.g., diabetes, osteoarthritis, depression) must first be addressed as this may also contribute to pain. The choice of intervention depends on the pain type.

Next, one must determine whether or not the patient's pain is acute or an exacerbation of a chronic complaint. This gives the clinician the initial tools to approach the rest of the patient's workup and possible interventions. If the patient reports exacerbation of a chronic complaint, an investigation of the device itself is warranted. Initially, the device representative should be contacted in order to interrogate the device and determine if there are any problems with the battery or leads themselves. If the interrogation of the device does not yield any clear etiology as to why the patient would be experiencing an acute flare of their chronic pain, it may be warranted to obtain imaging in order to determine if there has been any anatomical disruptions of lead placement. If imaging shows hardware malfunction or infection, neurosurgery may need to evaluate the patient and determine if any surgical interventions are warranted. General knowledge of the batteries for DBS is as follows and was adapted from the review article "DBS Programming: An Evolving Approach for Patients with Parkinson's Disease." [15]

> One of the first signs of a failing battery is worsening of symptoms. Therefore, knowing the estimation of battery life is critical. Battery drain is dependent on many factors including manufacturing tolerances, battery usage, battery chemistry, and variations in tissue impedance. The electrode surface area (small surface areas result in larger impedances) and the number of contacts used for stimulation affect the tissue impedance. Newer, rechargeable batteries have charge indicators reflecting battery life. Older systems operate within a particular voltage with the battery life starts at a voltage of 3.2–3.74 V with an end of life (EOL) reached when the battery drains to about 2–2.5 V. In general, batteries for DBS last on average 3–5 years.

If the battery is functioning appropriately, reprogramming the device may aide in therapy. Most deep brain stimulation (DBS) systems deliver stimulation using a

voltage-controlled pulse generator. For these systems, the amount of current delivered at the electrode will be affected by the impedance. Impedance of the electrode can varies over time, therefore the amount of current delivered through the electrode will also vary, and thus the voltage distribution generated in the target neural tissue will vary. The change in impedances could be partially responsible for the need to reprogram the stimulators but the effects are usually seen over a period of 3–6 months. Programming is usually not initiated immediately after the placement of a lead; instead a time frame of 2–4 weeks is allowed for the microlesion effects to fade away. These microlesion effects are believed to arise from the trauma of the DBS lead implantation rather than from the stimulation of the targeted brain structure. As a result, there is temporary improvement in clinical symptoms. Thus, for an accurate assessment of stimulation benefits, it is recommended that DBS programming gets initiated only when the initial benefits fade away [15].

If it has been determined that the new pain generator is an acute pain complaint, an investigation into that specific area of pain is warranted. Each physician should use their clinical judgement in accordance with the current guidelines surrounding the patient's complaint. One of the unique circumstances that should be considered in patients with DBS would be any alterations to the device due to trauma or other reasons such as infection. For example, there may be a patient with new onset neurological symptoms combined with new onset headaches and fevers that may warrant studies to determine if meningitis or hardware infection may be present. Otherwise, if the clinician determines that the DBS does not likely contribute to the patient's complaint while inpatient, it is reasonable to leave the device alone without interrogation and investigate other reasons the patient may have pain.

For the majority of patient with DBS, pain symptoms can be divided into five categories:

1. **Musculoskeletal** pain that affects the muscles, ligaments, tendons, joints, spine and nerves. These symptoms can be acute or chronic. Movement disorders are typically characterized by muscles that move uncontrollably, contracting and tensing for lengthened periods of time. Extreme conditions can involve the muscles that flex the neck, limbs and trunk creating abnormal postures and gestures that not only cause discomfort and disfigurement, but severe pain. Patients are also at risk for osteoporosis, "frozen" joints, and orthopedic fractures as most have low bone density or deconditioning secondary to lack of weight-bearing exercise and poor calcium and vitamin D intake. The first lines of treatment for musculoskeletal pain can be heat and cold packs and nonsteroidal anti-inflammatory drugs alone or in combination with acetaminophen [16].
2. **Neuropathic/radicular:** Some patients can experience severe postural changes with extreme leaning forward or to one side. This can lead to changes in the spine expediting disc degeneration, compression fracture, facet hypertrophy, or neuroforaminal stenosis causing radicular symptoms. For neuropathic pain, anticonvulsants such as gabapentin (Neurontin, Gralise, others) or pregabalin (Lyrica) can be effective. As second-line therapy, tricyclic antidepressants may be effective. However, caution must be taken as the anticholinergic effects (e.g., confusion, dry mouth, urinary retention, or constipation) may increase risk for falls or worsen symptoms patient may already be experiencing [16].

3. **Dystonic:** sustained or repetitive muscle twisting, spasm or cramp or rigidity that can weakened muscles or cause involuntary muscle contractions which can lead to painful deformities. Oromandibular dystonia, cervical or spasmodic torticollis, or limb dystonia affecting the upper and lower extremities can all produce painful conditions. For dystonic pain, adjustment of dopaminergic medications is particularly critical. The use of muscle relaxants have shown to be beneficial; however, if dystonia consistently occurs in one particular body part, botulinum toxin injections also can be helpful. The goal of botulinum toxin injection is to weaken the muscle enough to stop the abnormal contractions and twisting, but the patient may lose function in the body part as a result (e.g., foot drop). Thus, patient counseling is important to manage expectations [16].
4. **Akathisia:** causes the feeling of restlessness or inability to be still. Akathisia may be due to an imbalance between the central dopaminergic and β_2-adrenergic systems. Therefore, a possible treatment options could be to block the β_2 receptor. A blinded study has shown propranolol to be more efficacious than lorazepam only in neuroleptic-induced akathisia [3]. Presently, there is no definitive treatment for akathisia [17].
5. **Central pain:** neurological condition caused by a dysfunction that affects the central nervous system and is resistant to treatment. Central pain is the most difficult type of pain to treat. Antidepressants (selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or atypical antidepressants) or anticonvulsants (gabapentin or pregabalin) may be helpful. In select cases, opioids may be necessary [16].

4.3.1 Pain Assessment Tools

There are many types of pain assessment tools and scales one can use in order to ascertain a pain rating. The Visual Analog Scale, McGill Pain Questionnaire, numeric pain scale, among others may be used to help guide management. Unique to this population may be the association of cognitive impairment or dementia. Approximately 25–30% of all patients with Parkinson's disease also have dementia, but after having Parkinson's disease for 15 years, the prevalence of PDD increases to 68%. It has been observed that certain aspects of cognitive performance may decline after DBS, namely when the therapeutic target is the widely used subthalamic nucleus. This implies that DBS produces effects both on motor and cognitive neural networks, probably due to the fact that the targeted nuclei are also involved in associative processes, thus explaining the impact of DBS on cognition [18]. The following pain scales are available for providers to assess patients with dementia. https://www.nature.com/articles/nrneurol.2012.53 [19]

Self-report

- Present Pain Intensity (PPI) scale, report of pain experienced now versus last week

Caregiver or informant rating

- Pain Assessment for the Dementing Elderly (PADE) and global staff rating
- Pain Assessment Instrument in Noncommunicative Elderly persons (PAINE)
- Abbey Pain Scale

Observational rating

- Discomfort Scale for Dementia of Alzheimer's Type (DS-DAT)
- Checklist of Nonverbal Pain Indicators (CNPI)
- Pain Assessment in Advanced Dementia (PAINAD)
- Elderly Caring Assessment 2 (EPCA-2)
- DOLOPLUS-2
- Non-communicative Patient's Pain Assessment Instrument (NOPPAIN)
- Mobilization-Observation-Behaviour-Intensity-Dementia (MOBID-2) Pain Scale
- Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC)
- Dutch-translated Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC-D)

Interactive rating scale

- Assessment of Discomfort in Dementia (ADD) Protocol

While there are many instruments available, there is conflicting data as to which scale is most effective at determining how much pain a patient is experiencing. However, the current recommendation is that two scales are used to guide management and determine the effectiveness of any interventions or treatments. According to Corbett et al., the MOBID-2 scale is a thorough tool in combination with another scale of the provider's choice in the management of patients with dementia [20].

4.4 Challenges in the Management of Patients with DBS While in the Hospital

The management of patients with DBS can be complicated for many reasons. The patients can have movement disorders, polypharmacy, advanced age, dementia, and other medical issues that may limit treatment options. Identifying the patient's type of pain and using a multimodal treatment approach will be most effective at managing the patient's pain in an acute setting. If the patient has a DBS specifically for intractable pain, making sure the patient has enough psychiatric and psychological support will be important in long term management. Also, careful management of any other comorbidities that may exacerbate pain states (insomnia, depression, obesity, etc.) will be important while in the hospital.

4.5 Deep Brain Stimulation Medical Safety Issues

Frequently, a provider can be consulted for unique considerations not pertaining to pain or exacerbation of symptoms but for medical safety concerns in regard to the device. The following section outlines recommendations for proper management of a DBS if the patient is to undergo imaging, invasive or non-invasive procedures. The decision to program a patient's neurostimulator to the OFF state in order to perform medical diagnostic or therapeutic procedures should be carefully considered based on the patient's underlying medical condition. Consultation with the appropriate medical professionals (prescribing and implanting clinicians) is suggested. Regardless if the system is functioning properly or not, exposure to an electrical field, i.e. from electrocautery, can cause electrical currents to flow through the device and cause unintentional injury to the patient or damage to the device. Prior to any surgical procedure, it is recommended to be turned OFF the device and turn the voltage to zero, if applicable. Abrupt cessation of stimulation can result in a rebound effect of symptoms, so coordination prior to an elective procedure is ideal. Document the current settings prior to turning off the device as electrical current can revert the device back to the default settings. Similar to cardiac pacemakers, during surgical procedures utilize bipolar electrocautery if possible, avoid direct contact of leads and battery, and if monopolar cautery is required, minimize the cautery power settings, use short, intermittent bursts and place the grounding pad as distal from the device. Following the procedure, an interrogation of the device is warranted to ensure proper functioning. Cases that should be avoided are Lithotripsy (treatment for kidney stones), Diathermy (energy/heat direct therapy), Transcranial Magnetic Stimulation (TMS), and Electroconvulsive Therapy (ECT) may damage the neurostimulator circuitry and cause tissue damage resulting in severe injury or even death. All other cases that are not using electrocautery such as Colonoscopy or Cataract surgery are considered safe and risk benefits should determine if the DBS is placed in an OFF state.

Magnetic resonance imaging (MRI) of patients with implanted deep brain stimulation (DBS) devices poses a challenge for healthcare providers. Safety issues such as magnetic field interactions with the device can lead to component migration, induced electrical currents and tissue heating. In some cases, these issues can be avoided by the use of alternate neuroimaging modalities such as computerized tomography and transcranial Doppler ultrasonography, but there are clinical scenarios in which MRI is mandatory. Ultimately, the device is conditional. Current recommend are as follows but you should always check with the manufacture prior to imaging:

- Only 1.5-tesla horizontal-bore MRI should be used for scanning patients
- Only a transmit/receive head coil should be used
- Correct patient weight should be entered into the MRI console for calculating the head SAR correctly
- MRI parameters that allow average head SAR below or equal to 0.1 W/kg should be used
- The gradient dB/dt should be less than or equal to 20 T/s [20].

All other imaging modalities, including ECG (electrocardiogram) and EEG (electroencephalogram) are considered safe but may need to be turned off to limit interference.

4.6 Medications to Avoid

The most common reason for a patient to have an implanted DBS is for Parkinson's disease. Other comorbidities may exist in the population with DBS, and thus requires a comprehensive medication reconciliation to ensure polypharmacy does not result in medication interactions that may worsen symptoms or cause serious adverse effects. For pain related medications specifically, tricyclic antidepressants should be avoided as it can cause hypertensive crisis and dyskinesia in conjunction with levodopa. Also, anti-dopaminergic drugs and dopamine depleting drugs should be avoided as to not exacerbate any Parkinson's disease symptoms. MAO inhibitors may also cause hypertensive crisis and dyskinesia. Antipsychotic agents such as the phenothiazines should be avoided as they may worsen Parkinson's related symptoms. Other anti-dopaminergic medications such as metoclopramide should also be avoided [21].

4.7 Discharge Plan for Pain Management

Regular follow up after discharge may be necessary for patients with a DBS. If the DBS was initially placed for intractable pain, frequent follow up with frequent adjustments to the stimulator may be needed to obtain consistent pain control. Under these circumstances, it may be beneficial for the patient to follow up with their neurologist or neurosurgeon (whoever is managing the device) in order to obtain adequate, consistent pain control after discharge from the hospital. If the patient's pain does not stem directly or indirectly from the DBS itself, follow-up on an as needed basis may be justified. As always, clinical judgement for each individual patient is needed to determine the type and duration of follow up after discharge from the hospital.

4.8 Summary

- The management of patients with a DBS can be complicated due to our limited understanding of DBS in different pain states.
- DBS is used primarily for movement disorders and as an off-label therapy for intractable chronic pain, therefore a multimodal approach to treating patients' pain should be employed.

- A good understanding of a patient's chronic medical problems can help guide management. Patients with movement disorders often are elderly, suffer from depression, have chronic pain issues related to their disease (e.g. postural abnormalities leading to chronic pain), and other unique problems.
- An understanding of the specific type of pain (musculoskeletal, neuropathic, akathisia, dystonic, central) may help guide therapy in these patients.
- Special considerations may be needed for patient-specific comorbidities that may occur in patients with a DBS. An example would be using an appropriate pain scale in patients with dementia to guide management effectively.
- Imaging or consultation to neurosurgery may be indicated if the patient's pain is related specifically to the DBS device.
- Use a multidisciplinary approach when treating pain (including psychological support, regional anesthesia when possible, infusion therapy, non-opioid medications and opioids as indicated) with paying attention to medications that need to be avoided.

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Chapter 5
Patient with a Vagal Nerve Stimulator

Michael Suer and Alaa Abd-Elsayed

5.1 Introduction

The patient with medical devices such as vagal nerve stimulator can present diagnostic and treatment dilemma for even the sharpest of clinicians. In the workup and management of such patients, it is important to understand the underlying mechanism of the device and the disease pathophysiology in addition to the presenting complaint. Further, medical devices bring an additional complexity in the limitations of work-up permitted within the parameters of the device itself. This chapter will present the current medical understanding of the diagnosis and workup as well as a summary of some current evidence-based management options for the patient treated with vagal nerve stimulation (VNS).

The history of VNS dates to the 1880s, a transcutaneous electrical stimulator was developed to be applied over the carotid artery for both prophylactic and abortive treatment of seizures upon the basis that seizures were induced by excess blood flow to the brain and bilateral carotid artery compression aborted procedures. Bailey and Bremer [1] in 1938 reported vagal stimulation caused electro-encephalogram changes. In 1951, Dell and Olson [2] demonstrated that stimulation of severed cervical vagus nerve evoked responses in the ventroposterior complex and intralaminar regions of the thalamus. Then, in 1985, Zabara et al. [3] revealed electrical stimulation of the vagus nerves produced inhibition of the neural process, altering brain electrical activity and terminating seizures. Building upon this base of research and

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successful first human implantation in 1988, VNS has been utilized for patients in various clinical conditions.

5.2 Pathophysiology

In understanding the workup and management of pain in individuals with a VNS, understanding the vagus nerve and the mechanism of action and uses of a VNS technology is imperative. The vagus nerve is constituted of 80% afferent sensory fibers that relay visceral, somatic, and taste sensations while the remaining 20% of fibers are efferent [4–6]. The afferent fibers follow a path from the thoracic and visceral abdominal organs alongside the esophagus and bilaterally in the neck bundled with the carotid artery rostrally through the nucleus tractus solitarius terminating in higher cerebral centers including the locus ceruleus, dorsal motor nucleus of the vagus, medulla, amygdala, hypothalamus, parabrachial nucleus, and the thalamus [7–9]. Norepinephrine, a neurotransmitter key in controlling seizure threshold and mood regulation is found in high concentration in the locus ceruleus [10]. The efferent fibers are parasympathetic fibers innervating the heart, lungs, and gastrointestinal tract though the extent of the innervation remains incompletely known. The left vagus nerve (frequently used for VNS to avoid bradycardia) innervates the atrioventricular node whereas the right vagus nerves innervates the sinoatrial node. While rare following placement, bradycardia and arrhythmias can occur during intraoperative placement of the device primarily via retrograde stimulation.

While the exact mechanism of VNS has not been fully elucidated, proposed mechanisms include:

- Alteration of epinephrine release by projections of solitary tract to locus coeruleus in the medulla oblongata [11]
- Evaluation of gamma aminobutyric acid (GABA) levels in the brain stem
- Inhibition of aberrant cortical activity by reticular formation in the brain stem [12]
- Desynchronizing electroencephalographic activity [13, 14]
- Blood flow alterations [10]

While much of the neuroanatomic research regarding the underlying mechanism of action has been elicited for understanding seizure control, it appears the limbic system is equally involved via similar connections in the control of depression [15].

Indications for vagal nerve stimulation should also be understood in treating individuals who present for inpatient pain consultation who are being treated with VNS. Of the 2–5% of the worldwide population with epilepsy, approximately 5–30% of these have medically refractory complex partial seizures [16]. Approved in 1997 as an adjunctive therapy for adults (now approved for children at least 4 years old) with focal seizures, VNS is an option to reduce the severity and shorten the duration of seizures in those patients who remain refractory despite optimal drug therapy or surgical intervention. It can also be used in individuals with

debilitating side effects of antiepileptic medications. While initially approved in adults, it has also shown to be beneficial in children with refractory seizures. Despite a relative paucity of patients who become seizure free, there is a reduction of 50% of seizures in 50% of patients with treatment refractory partial complex seizures and the patient may have some control over seizures by hand-held magnets.

Major depression with a lifetime prevalence of 13% and 12-month prevalence of 5% has demonstrated nearly 75% of individuals will have a recurrent episode and many will not achieve remission. Further, about 30% of those suffering major depression fail first antidepressant therapy and 20% become resistant to combination therapy, psychotherapy, and electroconvulsive therapy [17]. FDA approved in 2005 for treatment-resistant depression, VNS has demonstrated efficacy in treatment via multiple measures. A review of 18 studies reported reduction of greater than 50% in the Hamilton Depression Rating Scale from baseline in a 10-week follow-up and 27–58% in 12-month follow up [18].

VNS consist of surgically implanted components and external components which communicate with the device (Fig. 5.1). A pulse generator houses a battery and electronic components that regulate the stimulation parameters and is typically implanted in the left upper chest wall just below the clavicle or in the left axilla and provides stimulation via the lead. While traditionally a dual pin model, newer models have been compatible with single pin leads. Connected to the pulse generator, a wire (lead) is wrapped around the left vagus nerve. The lead consists of helical contacts with an anchor to minimize the risk of lead migration. An external programming wand is a hand-held device held over the pulse generator as needed that transmits programming and interrogation information between the VNS therapy computer and the VNS pulse generator. A separate physician programmer is a laptop computer or hand-held device which connects to the programming wand and

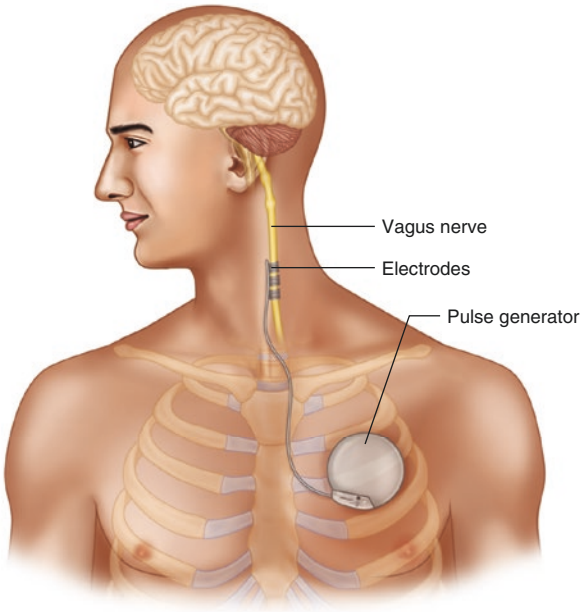

Fig. 5.1 Vagus nerve stimulator components

runs the VNS programming software. Similar to other stimulation modalities, one is able to change pulse width, amplitude, frequency, and duration of stimulation. Finally, the patient's magnet is worn by patients enabling them to reset the pulse generator, test daily function, temporarily inhibit VNS, or provide on-demand therapy [19].

VNS is currently being explored as a treatment for a variety of other autoimmune and chronic inflammatory conditions as early clinical studies have demonstrated VNS may attenuate the inflammatory response through activation of the cholinergic anti-inflammatory pathway [20]. Inflammation is implicated in many chronic diseases including cardiovascular disease, arthritis, Alzheimer's disease, rheumatoid arthritis, Crohn's disease, irritable bowel syndrome, and fibromyalgia. However, the efficacy of VNS in these disorders remains under investigation. In addition, VNS was also found to have effects on the serotonergic and noradrenergic neural circuits. Lange et al. [21] conducted a Phase I/II clinical trial of VNS as an adjunct treatment for patients with fibromyalgia based on previous studies demonstrating efficacy for VNS to treat depression. After 11 months, 7 of the 12 patients had effective relief of symptoms based on minimum clinical difference of their pain symptoms. Barbanti et al. [22] examined 50 patients with migraine treated with externally-applied VNS in two 120-s intervals with 3 min between. Of these, 56 and 64% reported pain relief at 1 and 2 h, respectively. Similarly using non-invasive VNS, Silberstein et al. [23] performed the ACT1 study at the neck to treat cluster headaches. This study suggested non-invasive VNS can be successful to treat episodic cluster headaches. While these results further research with larger, multicenter, randomized trials; they present evidence for VNS in treating fibromyalgia and headaches.

5.3 Diagnosis

Complications and failure of the device are a rare event and can result from lead fracture, device malfunction, disconnection, or battery end of life and can result in a variety of symptoms. Should the device be suspect of malfunction, the device will need to be interrogated and assessed for lead continuity. Should the treating physician not have availability or expertise with using interrogating devices, the managing provider should be contacted in order to ensure correct evaluation of the device. If lead fracture is suspected due to trauma or other event, x-rays could be obtained to check for fracture in an expedient fashion. If there are positional or other patient-reported conditional aspects to the symptoms, the device can be interrogated in the aspect of symptom presentation in order to effectively interrogate the device.

Adverse effects from stimulation tend to be quite rare and are often identified soon after implant if they are not first discovered during the intra-operative placement of the VNS. The most common adverse effect was voice hoarseness or alteration during stimulation though the incidence and intensity can be related to intensity of stimulation. Similarly, coughing and pharyngitis can be related to the intensity of the output current. Other less common adverse effects of VNS include but are not

limited to headache, neck pain, dysphagia, dyspepsia, nausea, paresthesias, and heart palpitations [24]. In the case of heart palpitations, it is important to identify the laterality of the VNS as stimulation of the right vagus nerve can cause bradycardia. With each of these adverse effects, initial approach if VNS is suspected as the cause of the symptoms, turning the device off or halting stimulation should provide at diagnostic confirmation of the device's contribution to the symptoms. Should this alleviate the symptoms, follow up should be arranged with the VNS implanting provider to initiate definitive treatment should the device need to be removed. Further, continued communication and follow up with the managing provider should be arranged to ensure appropriate treatment of the underlying condition.

Should the VNS be turned off and the patient continue to have symptoms, one must return to their education of the non-device related medical conditions that could produce the presenting symptoms (e.g., chest palpitations worked up as potential cardiac etiology). It is common in today's society of medical devices to assume primarily that medical complaints are due to device malfunction rather than to rely on a thorough history and physical exam that presents high pre-test probability of the disease pathology. In these scenario's, it is most useful to view the device as simply another diagnosis in the differential diagnosis that is established with likelihood of device-related symptoms based upon the patient's presenting symptoms.

5.4 Treatment

As VNS is primarily used for seizure management, we will discuss situations in which the VNS is unavailable or the patient continues to have seizures despite VNS therapy. Examining the treatment options in patients treated with VNS really falls into two broad categories—seizure management and seizure prevention. In this scenario, with a focus on pain management, we will examine the methods that can be utilized for pain that will not affect seizure threshold.

Whether taught as non-maleficence, *primum non nocer*, or "first, do no harm," this basic tenant is fundamental to the practice of medicine and is taught in medical school throughout the world. As such, in treating these individuals, we must avoid situations in which seizures could be induced. Certain conditions that increase the risk of seizures include head trauma, brain tumor, stroke, intracranial infection, anorexia nervosa, and other congenital abnormalities.

One of the more common medications used for acute pain include opioids. Seizures can be precipitated by opioids in patients with a preexisting seizure disorder. The incidence of these effects during many opioids is not known, but appears to be rare at normal doses. In particular, rapid administration of high dose opioids may transiently elevate intracranial pressure and reduce cerebral perfusion pressure. However, caution must be exercised in particular with tramadol and fentanyl as both can interact with either other medications or underlying pathology to lower the seizure threshold or induce seizure activity. Tramadol should be used cautiously in

individuals with pre-existing seizure disorders, metabolic disorders, increased intracranial pressure, CNS infection, head trauma, and in those who are experiencing alcohol or illicit drug withdrawal. Medications known to interact with tramadol with resultant decrease in seizure threshold include: bupropion, naloxone, carbamazepine, phenytoin and postherniation, haloperidol, loperamide, non-ionic contrast media, topiramate, and quetiapine among others less commonly used. Note that in tramadol overdose, naloxone administration may increase the risk of seizures. Fentanyl must also be used with extreme caution in patients with CNS depression, head trauma, brain tumors, or increased intracranial pressure.

Other medications commonly cited to lower the seizure threshold include, but are not limited to [25]:

- Antidepressants
  - Bupropion
  - TCA's
  - SNRI's and SSRI's in rare scenario's (1–2% of affected patients) [26]
- Stimulants
  - Amphetamine
  - Dextroamphetamine
  - Methylphenidate
- All antipsychotics
- Acetylcholinesterase inhibitors
- Anticholinergics
- Antiemetics
- Antihistamines
- Baclofen
- ß-Blockers
- Cephalosporins
- Cyclosporine
- Dalfampridine
- Estrogen
- Imipenem
- Iodinated Contrast Dyes
- Isoniazid
- Lithium
- Local anesthetics
- Methotrexate
- Metronidazole
- Narcotics
- Penicillins
- Pyrimethamine
- Quinolones
- Tacrolimus
- Theophylline

Other medications such as gabapentin, pregabalin, and topiramate have also been utilized for pain, typically neuropathic type pain. While they have differences in mechanism of action and efficacy, each is categorized broadly as an anticonvulsant. Gabapentin blocks N-type calcium channels and is used for restless legs, neuropathic pain, and as an adjunct for partial seizures. Pregabalin is chemically and structurally similar to gabapentin with antiepileptic, analgesic, anti-convulsant, and anxiolytic properties. Also similar to gabapentin, it has found use for neuropathic pain and as an adjunct for partial onset seizures in addition to FDA-approved indications of fibromyalgia and diabetic peripheral neuropathy. Topiramate is an oral anticonvulsant in addition to a weak carbonic anhydrase inhibitor. While more frequently used for migraine prophylaxis, it has found use in some clinics in the treatment of neuropathic pain and can be used for both partial and generalized seizures. Each of these medications, however, require close monitoring for suicidal thoughts/behaviors and depression. In situations where VNS is utilized for treatment of refractory epilepsy, caution must be exercised with addition of an anti-seizure medication and advice should be sought from the treating epileptologist prior to initiating these medications for the treatment of pain.

Given the frequency and relatively high number of medications that can lower the seizure threshold, non-pharmacologic management becomes of utmost importance. As psychological distress has been demonstrated to exacerbate chronic pain symptoms, behavioral modalities are an important form of treatment. While often difficult on an inpatient setting, efforts can be made to assess the psychological well-being of individuals, especially those utilizing VNS for treatment of chronic pain and depression.

5.5 Pain Assessment Tools

Pain assessment is challenging in all situations, but in particular on the inpatient, acute setting. As such, appropriate assessment is an invaluable skill to develop for students and throughout our medical careers. While there are multiple validated pain and functional assessment tools, the majority of clinicians rely heavily on history, physical examination, and patient report. Within these parameters, pain can be categorized in a multidimensional approach by determining the following: onset and duration (mechanism or underlying inciting event if identifiable), location, distribution or radiation, exacerbating and relieving factors, and associated symptoms. However, I would advocate additional simple assessments including function impact on mood, ability to perform activities of daily living, and sleep. Often with the latter of these, we can utilize medications at night with a sedative side effect profile (e.g., gabapentin) that can help with both sleep and pain.

Further, one can assess the severity of pain via multiple parameters. By far the most common tools are numeric rating scale (“How bad is your pain on a 0–10-point scale”) and the visual analogue scale (having patient mark pain on a line drawn with scale of 0–100). Pain assessment can be further complicated by patient age and

ability to accurately convey pain. In the elderly, one can often encounter underreporting of pain due to wanting to avoid complaining or due to communication or cognitive impairment. Other medical comorbidities may also serve to overshadow pain complaints in many individuals. Additionally, decreasing in hearing and visual acuity may hinder our ability to accurately assess pain as some tools require extensive explanation or visualization to perform. The verbal descriptor scale may be the easiest tool for the elderly to use. It allows patients to use common words to describe what they are feeling [27].

At the other end of the spectrum, infants and children can also be difficult to assess although VNS is not indicated for patients under 12. Typically, children older than 3–4 years old can self-report pain. Factors that can influence pain that should be considered include limited cognitive or language skills. One should also consider the positive or negative consequences of a child's behaviors as they associate with pain. Children can, at times, underreport pain to avoid procedure or injections which can be used to treat pain as these can provide short-term discomfort they wish to avoid [27].

5.6 Challenges in Management of Pain While in the Hospital

Managing pain in and of itself is a challenging endeavor for all involved for myriad reasons. Adding in the complexity of an inpatient setting and medical devices only makes the struggle more perplexing. As eloquently discussed in other chapters (see "Patient with pancreatitis or organ related pain"), factors influencing pain range from mismanagement of acute pain, psychological effects, social issues, multiple sources of pain, medication side effects, and having multiple providers. However, specifically for patients with VNS a multi-disciplinary approach is of utmost importance.

Safety monitoring after implantation of medical devices is essential throughout the product's life cycle. Despite infrequent use for pain, VNS must be considered in the diagnosis and treatment of pain of other conditions. As most pain providers do not have expertise in the realm of VNS, the neurologist or neurosurgeon who is working with the patient should be alerted to the patient's hospitalization. Given the specialty equipment mentioned previously in this chapter to operate and interact with the VNS, it requires a certain level of competence and expertise to correctly manage the device. However, most companies also have representatives that can provide some guidance if the need arises. Further, given the patient's level inpatient complexity (ICU vs general floor), the patient often has enough knowledge of their device to assist and perform basic device functions (though one should not consider this as a definitive treatment plan).

Regarding work-up of other medical diagnoses, similar to other neuromodulatory devices, one must consider multiple factors on the safety of diagnostic work-up, particularly how it relates to obtaining advanced imaging. Similar to spinal cord stimulators, VNS began as non-MRI compatible devices. However, as technology

progressed, multiple companies began to explore obtaining MRI's in individuals with VNS. Initially, de Johng et al. [28] found that MRI's of the head and below the neck were deemed safe in the majority of patients. However, this excluded the area of the VNS. As technology has progressed, most companies now produce devices that are fully MRI compatible. As such, it is imperative to obtain correct device manufacturer and model in order to safely determine if an MRI is safe. The neurologist should always be consulted prior to any medical imaging, diagnostic test, or surgical procedure to ensure patient safety and device integrity. If deemed safe, there is also a protocol for each device outlining the steps in order to safely perform the required imaging. In many of these protocols, the VNS must be turned off and the patient is reminded not to bring their magnet to the MRI suite. If the patients notes any discomfort during the test, they should alert the technician and the MRI stopped. Following the MRI, the patient will return to the neurologist to have their VNS turned back on to stimulation mode. Given the most common indication for VNS at this time is seizures, should the patient have a seizure during the MRI, standard seizure protocol should be followed.

5.7 Management of Pain in the Inpatient Setting

Similar to other pain conditions, treating pain in individuals with VNS requires balancing several aspects of medicine including but not limited to pain intensity, type of pain, medical comorbidities, and drug interactions. The WHO [29] established an analgesic ladder for treating cancer pain but it can neglect the nuance of pain and is not necessarily designed for the treatment of acute pain. However, it provides a well-known basic framework for discussion of the treatment of pain. Mild to moderate pain should be treated with non-opioid pharmacologic agents such as NSAIDs and acetaminophen. The use of only one medication from an analgesic category is always recommended (i.e.; one NSAID instead of two or one opioid instead of two). For moderate to severe pain, short term opioid treatment can be beneficial; however multimodal approaches have become the standard amongst practitioners based on evidence and one should not exclude analgesics of lower steps on the ladder with the addition of medications higher on the ladder. The general rule of thumb is to administer several drugs if and only if they work by different mechanisms. Further, one must assess the type of pain a patient is exhibiting. If you suspect the patient has neuropathic type pain (often described as burning, pins/needles and numbness), analgesics such as gabapentin, pregabalin, or nortriptyline should be considered.

In addition to oral analgesics, one should consider interventional techniques when appropriate. One should keep a cache of pain management options when patients demonstrate pain refractory to more conservative measures. As with other pain conditions, more invasive techniques should be reserved for those individuals for whom conservative approaches have been exhausted or the clinical scenario necessitates.

While not always available inpatient, many other resources are available in the community setting and have their place in the treatment of pain. These include cognitive behavioral therapy and other psychotherapy modalities, Yoga, Tai Chi, acupuncture, physical therapy, and others. If not available, but the treating teams believes these modalities have possible efficacy in treatment for the patient, they can be discussed and even recommended upon discharge. It cannot be overstated that treatment of acute pain in an expedient and efficient manner is essential in the prevention of chronic pain upon discharge.

5.8 Discharge Plan for Pain Management

Once the inpatient with VNS is discharge, outpatient follow up becomes an important modality of treatment in and of itself. With lack of optimal discharge planning, patients may very well become "lost to follow up" with conditions requiring fairly prompt follow up. Ideally, follow up will be arranged prior to patient discharge though this can be difficult with weekend discharges. All attempts should be made to ensure clinic follow up with VNS managing physician and have both baseline and rescue medications provided depending on the clinical scenario in which the VNS is placed. In the cases of pain complaints, patients should have adequate medications such that no further refills will be required prior to outpatient follow up with the managing providers. In certain scenarios, establishing care with new providers is also warranted (e.g., patient with VNS for treatment of severe depression will need to establish with outpatient psychiatrist if not already established). Further, patients (especially those started on new medications or altered dosages of medication) should be thoroughly educated on the side effects and adverse reactions associated with their respective medications. Patients should also be provided adequate contact information for clinicians who should be contacted in given scenarios (e.g., VNS-managing provider should be contacted for symptoms possibly related to the VNS such as voice alterations, swallowing difficulties, etc.). Given the frequent multiple medical comorbidities seen in many of our patients today, they should also be encouraged to follow up with their primary care provider to monitor for overall health concerns. One must remember that the end of an acute medical condition does not end the patient's care but provides us with an opportunity to impact the patient as a whole and ensure appropriate follow up for optimal healthcare.

5.9 Summary

- Workup of the inpatient patient treated with vagus nerve stimulation must begin with a thorough history and physical exam.
- Investigations including imaging and labs should be performed based on the acuity of the situation.

- Regarding MRI's, there is significant variability in MRI-compatibility amongst devices. Attention must be made to the device model in order to determine MRI-compatibility of the device.
- Patients receiving treatment should be aware of all benefits, alternatives, and risks to which ever treatment modality is being considered. The goals of treatment should be reviewed with the patient.
- The treatment plan should be discussed with the entire treatment team and should be based on sound evidence-based data and established clinical practice. All efforts should be made to include the primary treating physicians who manage the VNS in the outpatient setting.
- Conservative non-pharmacological treatment options should be the forefront of any treatment plan.
- Pharmacological management choice should be based on patient preference, comorbidities, availability, cost, and side effect profile. Particular attention paid to avoiding medications that can exacerbate their underlying condition (e.g., avoid medications that can lower the seizure threshold in patients utilizing VNS for treated of retractable seizures)
- More invasive techniques should only be considered in patients whose pain is refractory to more conservative measures.
- Adequate pain assessment is an important tool when deciding on treatment modality and treatment necessity.
- Patients treated with VNS for intractable epilepsy should be treated with standard rescue medications should seizure activity be evident after cessation of VNS efficacy

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Chapter 6
Inpatient Pain Medicine Considerations in Patients with Heart Failure, Cardiac Arrhythmias, and Other Cardiac Conditions

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6.1 Introduction

Patients with heart failure, arrhythmias, and cardiac conditions are frequently encountered in the inpatient setting. These patients are medically complex and often have multiple comorbidities that must be taken into consideration when recommending potential medical and/or interventional therapies. It is not uncommon for cardiac patients to be on multiple different medications with potential drug interactions and to have end organ dysfunction as well. Furthermore, this patient population is at high risk for developing chronic pain at baseline which, while often challenging to treat alone, may be especially difficult to treat when they have recently undergone a procedure or operation [1]. For this reason, an expert pain consultant must appreciate these challenges and understand the complexity of treating both acute and chronic pain in this expanding patient population.

6.1.1 Heart Failure Overview

Heart failure is one of the main causes of morbidity and mortality in the world [2]. With modern day improvements in medical management, there has been an increase in life expectancy of patients diagnosed with heart failure as well as a substantial increase in health care cost. Heart failure affects more than 23 million patients worldwide, with an increasing incidence and prevalence in recent years [3]. It is estimated that roughly 5.8 million people suffer from heart failure in the United

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States alone. Furthermore, pain is a very significant issue in this patient population. The prevalence of pain in patients with heart failure varies widely in the literature, with some studies reporting its incidence as high as 85% [2].

In order to be an effective pain medicine consultant, it is important to understand the most recent changes in heart failure nomenclature and have a basic understanding of how heart failure is diagnosed and treated. The 2013 ACCF/AHA defines heart failure as a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood [4]. Heart failure is a clinical diagnosis made in patients presenting with certain symptomatology and physical exam findings suggesting vascular congestion and/or peripheral hypoperfusion. These finding are secondary to either a functional or structural cardiac abnormality [5]. Patients will frequently present with one or more of the following symptoms: coughing, fatigue, orthopnea, and/or paroxysmal nocturnal dyspnea. Common physical exam findings indicating heart failure include: cyanosis, jugular venous distension, peripheral edema, rales, and/or murmurs (i.e., S3 Gallop). Chest x-ray, echocardiogram, and laboratory findings (i.e., elevated BNP) can all be used to help solidify a diagnosis in patients presenting with these signs and symptoms [6].

Currently heart failure is divided into two categories: heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). HFpEF is defined as having a left ventricular ejection fraction of greater than or equal to 50%. HFrEF is defined as having a left ventricular ejection fraction of less than or equal to 40%. Patients presenting with ejection fractions between 40 and 50% fall into an intermediate category, where current recommendations for symptom management is not as well defined [5]. Medical therapy, dietary restriction, and life style modifications remain the mainstay treatment for patients with heart failure. Patients are frequently started on a beta blocker as well as either an ACE inhibitor or Angiotensin receptor blocker. These medications are usually started in the early stages of heart failure and are important in attenuating cardiac remodeling. Spironolactone is also commonly added to this medication regimen for patients with moderate to severe disease, as it has been shown to reduce mortality in patients with reduced ejection fractions. Lastly, diuretics are frequently used as patients' heart failure symptoms progress to help with volume overload. Diuretics have not been shown to reduce mortality, but have been shown to reduce hospital readmission rate and symptom management [6].

6.1.2 Cardiac Arrhythmias Overview

As a pain consultant, it is also important to have a strong understanding of cardiac arrhythmias and their implication on the management of pain. This disease state is associated with substantial morbidity, mortality, and healthcare costs. Cardiac arrhythmias are a broad diagnosis category that can be separated into atrial arrhythmias, ventricular arrhythmias, conduction system disease, and supraventricular arrhythmias. Atrial fibrillation is the most common arrhythmia

and has been estimated to affect approximately 2.3 million people in the U.S. alone. It is associated with an increase in both mortality and stroke [7]. Ventricular arrhythmias have been estimated to cause between 75 and 80% of sudden cardiac death cases, which account for up to 450,000 mortalities per year in the U.S [7]. While this type of arrhythmia is not as prevalent as atrial fibrillation, it is one of the more life-threatening pathologies [7]. As a result, pain consultants must take care when prescribing any medications to patients diagnosed with ventricular arrhythmias.

In general, the treatment of arrhythmias is complex and dependent on the type of arrhythmia. Basic arrhythmias are usually first identified in patients presenting with symptoms such as palpitations or syncope, and are often confirmed with a 12 lead EKG. Radio frequency ablation and pacemaker/implantable cardioverter-defibrillator (ICD) implantation are all common procedures performed in patients with cardiac arrhythmias. Medications such as beta blockers and antiarrhythmic are also commonly prescribed [8]. It is important to have an understanding of basic cardiac medications and how they relate to commonly prescribed pain medications. Multiple different pain medications have been shown not only to cause electrolyte abnormalities, but also to cause irregular cardiac rhythms. This in turn can either precipitate or worsen underlying arrhythmias.

Drug metabolism is another important topic when treating patients with cardiac arrhythmias. For example, methadone has been shown in a retrospective study to significantly prolong QTc intervals (>500 ms) in more than 16% of patients, with 3.6% of these patients ultimately presenting with torsades de pointes [9]. Furthermore, methadone is metabolized by the CYP3A4 enzyme. Amiodarone, diltiazem, and verapamil are frequently prescribed medications for cardiac arrhythmias. All of these medications inhibit the CYP3A4 enzyme, potentially leading to increased levels of methadone and subsequently increasing patients' risk for QTc prolongation and potential torsades de pointes (this will be discussed further in the *Treatment* section of this chapter) [10].

6.1.3 Importance of Pain Control

While most physicians recognize the importance of medication compliance and lifestyle modifications when treating patients with cardiac disease, the physiologic ramifications and increased morbidity and mortality associated with uncontrolled pain is often overlooked. Gan et al. found that all cause and cardiac mortality was significantly higher in heart failure patients with moderate to severe pain (defined as pain scores greater than 4) than those patients with mild pain (pain scores less than 4). Length of stay (8.04 vs 3.25 days) as well as readmission for myocardial infarction, heart failure exacerbations, and strokes (0.36 vs 0.21) have also been shown to be significantly elevated in patient with a diagnosis of heart failure with associated pain. Furthermore, it has been shown that there is an increase in major adverse cardiac events (MACE) and a decrease in quality of life (QOL) in patients with heart failure who have moderate to severe pain [11].

The psychological impact of patients suffering from chronic pain has also been shown to adversely affect their heath. There is an increased incidence of anxiety, depression, feeling a loss of control over one's life, and a feeling of being a burden to family in individuals reporting pain [12]. Patients suffering from anxiety and depression also have a lower incidence of overall medical compliance, as well as exercise and diet compliance. Medical compliance is extremely important in patients living with heart failure. Proper medication, dietary, and exercise compliance not only decrease the frequency and severity of heart failure exacerbation, but also improve long term clinical outcomes [13].

6.2 Pathophysiology

The etiology of pain in patients with cardiac conditions is currently thought to be multifactorial. It is most likely related to ischemic, neuropathic, and inflammatory mechanisms. There is most likely a psychological component as well that affects how patients not only perceive their pain, but also how they cope with it. Depression, anxiety, fatigue, and hopelessness are all common comorbidities associated with chronic cardiac conditions and play an important role in pain [2].

6.2.1 Source of Pain

Inflammatory mediators and cytokines are likely involved in the generation and modulation of pain. Gan et al. looked at the relationship between pro-inflammatory cytokines and the incidence of pain in patients with heart failure. They found no significant difference in serum levels of NT-proBNP, IL-6, and IL-10 in patients with pain and patients without pain. However, they did find a significant elevation in serum levels of TNF-**α** in heart failure patients who experienced symptoms of pain [11]. TNF-**α** has been implicated in the induction of both allodynia and hyperalgesia. Schäfers et al. found TNF receptor (TNFR) stimulation to be involved in the sensitization of sensory neurons after peripheral nerve injuries. These findings suggest that TNFR plays an important role in the maintenance of neuropathic pain [14]. While the exact mechanism of pain transmission is unclear, these studies indicate that TNF-**α** as well as other cytokines and inflammatory mediators are likely involved in the transmission of pain in patients with cardiac disease.

Hyperglycemia, not unsurprisingly, has also been shown to be associated with an increased incidence of pain in heart failure patients [11]. Diabetic neuropathy can be a common comorbidity in cardiac patients and it has been hypothesized that the production of superoxide molecules and subsequent cytosolic and mitochondrial oxidative stress is implicated in diabetic neuropathy. The peripheral nervous system, Schwann cells, and microvascular endothelium are all particularly susceptible to inflammatory and oxidative damage [15].

6.2.2 Cardiovascular Consequences of Poor Pain Control

It is important to understand why good pain control is beneficial to the overall health of cardiac patients as well. Anybody who has worked in the field of medicine knows that patients in pain usually have an increase in both their heart rate and blood pressure. The two basic mechanisms involved in this phenomenon are sympathetic/autonomic stimulation and release of adrenalin from the adrenal glands. Hypertension and tachycardia are harmful to patients with coronary artery disease, heart failure, and arrhythmias. There have even been case reports of patients experiencing angina during acute pain flairs that resolved after their pain was controlled. Furthermore, chronic pain induces a "stress-like" state in the body causing the release of stress hormones such as cortisol. Cortisol induces both hyperglycemia and hyperlipidemia, both of which are known risk factors for coronary artery disease [16]. Liu et al. studied the effects of chronic stress on the progression of pressure overload induced cardiac dysfunction in animal models. They found higher levels of norepinephrine induced cardiomyocyte hypertrophy and apoptosis, cardiac fibroblast proliferation and collagen expression in rats exposed to stress [17]. This would suggest that chronic stress states such as pain can be extremely harmful to patients with heart disease.

6.3 Risk Factors

As a consultant physician, it is important to understand which cardiac patient populations are most susceptible to suffering from poorly controlled pain. Gan et al. found female gender, hyperglycemia, more comorbidities, lower LVEF (≤40%), and poorer exercise capacity to be associated with symptoms of pain in heart failure patients. They did not identify any statistically significant increase in pain scores associated with age and other sociodemographics [11]. These findings were supported by several other studies which also found there to be an increased incidence of pain in patients with more co-morbidities, lower LVEF (≤40%), and poor functional capacity [2]. This would suggest that pain is not only a symptom of heart failure, but may also potentially be an early indicator of disease or proxy for disease severity. Goodlin et al. also conducted a study looking at pain prevalence, location, character, severity, frequency, and correlates in patients with advanced heart failure. They found that there was a statistically significant association of degenerative joint disease, depression, shortness of breath, angina, and non-degenerative joint disease arthritis with increased levels of pain [18].

Psychiatric co-morbidities, social support, and personal relationships also seem to contribute to how patients experience pain. It is estimated that approximately one-third of patients with heart failure suffer from anxiety and depression. Studies have shown that a diagnosis of major depressive disorder after heart failure is a predictor of both all-cause mortality and cardiovascular mortality [19]. There is also a clear relationship between higher levels of pain and depression/anxiety [2].

6.4 Diagnosis

Diagnosing pain in patients with cardiac conditions can often be difficult. It involves first identifying the source of pain, which can vary from patient to patient and is frequently related to their other comorbidities. Patients with cardiac disease frequently have other health problems such as peripheral vascular disease, chronic obstructive pulmonary disease, cancer, pneumonia, diabetes mellitus, depression, anxiety, osteoarthritis, and low back pain, all of which can contribute to their overall pain [2]. These factors, along with the patients' underlying cardiac condition, must be taken into consideration when assessing and diagnosing patients' pain.

The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [20]. This is a relatively broad definition that should be broken down further. Total pain was first described by Dr. Cicely Saunders in relation to patients who experienced pain at the end of life. Her definition can also be applied to patients living with chronic life-threatening illnesses such as heart failure, cardiac arrhythmias, and other cardiac conditions. She described total pain as the sum of physical, emotional, social, and spiritual pain [21]. While the emotional, social, and spiritual components of pain are important to the holistic treatment of pain, for the purpose of this chapter we will focus on the diagnosis and treatment of physical pain.

Physical pain can be separated into two major categories: neuropathic pain and nociceptive pain. Neuropathic pain is defined as pain related to either direct or indirect damage to the peripheral or central nervous system [21]. Neuropathic pain is typically characterized as burning, shooting, stabbing, or tingling pain. Patient will classically describe it as a "pins and needle" or an "electric shock" sensation. It may be associated with dysesthesia, which is an unpleasant abnormal sensation, or allodynia, which is pain generated from stimuli that are usually non-painful. Neuropathic pain can be either episodic or continuous in nature [1]. An example of neuropathic pain in a cardiac patient would be a patient with poorly controlled diabetes experiencing diabetic neuropathy.

Nociceptive pain on the other hand is the result of actual or threatened damage to non-neuronal tissue. Transmission of nociceptive pain is through the activation of nociceptors. Activation of these receptors can be caused by either inflammation or direct trauma to tissues [21]. Nociceptive pain can be broken down into three primary categories: superficial, somatic, and visceral. Superficial pain is the activation of nociceptors in the skin or superficial tissue. It is characterized as sharp and well-defined pain. An example of superficial pain in a cardiac patient could be recent incisional pain from a minor procedure (i.e., pacemaker or ICD implantation). Somatic pain is the result of the activation of nociceptors on musculoskeletal tissue such as bones, muscle, ligaments, and tendons. It is characterized as dull, aching, and poorly localized pain. An example of somatic pain in a cardiac patient would be someone who recently underwent coronary artery bypass grafting (CABG) and was suffering from post-sternotomy pain. Lastly, visceral pain is the result of ischemia,

stretch, or inflammation of visceral organs. It is characterized as a dull, pressure-like, diffuse pain and can be associated with nausea, vomiting, and malaise [1]. An example of visceral pain in a cardiac patient would be angina associated with coronary artery disease or bowel ischemia with peripheral vascular disease.

Distinguishing between nociceptive and neuropathic pain is often challenging, but it is important to properly diagnose which type of pain a patient may be experiencing, as the treatment options may differ for each. A basic sensory examination can be one of the best tools to help to characterize a patient's pain. Sensory nerve fibers that are assessed with this examination include A-beta touch fibers (i.e., assessing sensation with fingers/cotton), A-delta "fast" pain fibers (i.e., assessing pain with a straight pin or broken wood tongue depressor), and C "slow" pain fibers (i.e., assessing thermal sensation with a warm compress). It is often helpful to compare the suspected pathological site to the contralateral extremity or another unaffected body part [22].

Gathering a thorough history and ascertaining both the type and location of pain also play a critical role when assessing and diagnosing patients. Cardiac patients are more prone to experiencing pain in certain areas of the body. Goodlin et al. looked at the incidence of pain in patients with heart failure and found the most common site of pain to be located in the legs below the knees (38.2%), followed by lower back pain (30.7%). Furthermore, they found that most patients complained of experiencing pain in multiple sites (39.5%). Interestingly, the most common site, pain below the knees, was not correlated with a clinical assessment of edema or elevated volume status. Angina pain was also a common complaint among patients [18]. Headaches appear more frequently among heart failure patients than non-heart failure patients as well [2]. A pain consultant should keep these common sites in mind when gathering a medical history, as they may uncover potential sources of pain in the cardiac patient.

6.5 Treatment

The primary goal of pain control in the inpatient realm is to provide optimal patient comfort in the setting of their comorbid disease processes. The secondary goal, which is especially pertinent to patients with cardiovascular disease, is attenuation of the physiologic responses to pain, including hypermetabolism, increased oxygen consumption, hypercoagulability, and alterations in immune function, among others [23]. Finally, attention to and management of acute pain helps prevent the development of chronic pain. In patients with cardiovascular disease, multimodal pain management aids to minimize unwanted side effects while adequately providing analgesia in a susceptible population. The multimodal armamentarium includes opioids, acetaminophen, ketamine, neuropathic pain medications (anti-depressants, calcium-channel ligands), as well as regional anesthesia. Scenarios of commonly encountered pain states and treatment options in the setting of pre-existing cardiovascular disease are addressed below:

6.5.1 Scenario 1: Management of Acute-on-Chronic Back Pain Following a Lumbar Laminectomy on the Post-operative Acute Care Floor

Back pain is one of the most commonly encountered pain states, with up to an estimated 84% of adults experiencing lower back pain at some point in their lifetime [24]. For patients with chronic back pain, the most common etiologies include damage of the spinal nerve roots from vertebral degeneration leading to radiculopathy or spinal stenosis secondary to arthritis. Laminectomy procedures decompress neural elements in the setting of radiculopathy secondary to degenerative disc disease [25]. In cardiovascular disease, adequate acute pain control post-operatively is imperative to maintain hemodynamic stability and prevent oxygen consumption/delivery mismatch, worsening pre-existing coronary artery disease. In the post-operative period, multimodal pain control can be employed, balancing opioids with ketamine, acetaminophen, and lidocaine infusions, among others. Using adjunctive agents allows for a lower effective dose of opioids, minimizing undesired effects such as over-sedation, decreased respiratory drive, delirium, hypotension, ileus, nausea/vomiting, and the development of tolerance.

Patients may require intravenous formulations of opioids initially for their faster onset of action. Patient-controlled analgesia or a PCA delivery of morphine, hydromorphone, or fentanyl has the benefit of decreased delay in patient access to pain medication, less likelihood of overdose with a fixed lockout period, and an ability to titrate. In general, opioids have little effect on hemodynamics, making it useful in the setting of heart disease. However, close patient monitoring is essential to avoiding hypoventilation and subsequent hypercarbia, which can have detrimental effects in heart failure (discussed further below, in *Management of pain in the inpatient setting*). Ketamine provides analgesia by blocking *N*-methyl-D-aspartate (NMDA) receptors, reducing glutamate release, and via binding to sigma-opioid receptors [26]. Ketamine can be useful in reducing the total opioid dose required by a patient. Low-dose ketamine has not been associated with adverse pharmacologic effects on respiration or cardiovascular function in healthy patients [27]. Again, ketamine should be used with caution, especially in those with heart failure (discussed further below, in *Management of pain in the inpatient setting*).

Systemic lidocaine can be a useful adjunctive therapy in the acute pain setting. Intravenous lidocaine works by attenuation of peripheral nociceptor sensitization and central hyperexcitability via its sodium channel blocking action. Additionally, IV lidocaine has potent anti-inflammatory properties, decreasing circulating cytokines, which contribute to its analgesic properties [28]. Specifically in the realm of complex spine surgery, IV lidocaine has demonstrated significant post-operative pain control [29]. However, careful attention should be paid to signs of toxicity or developing dysrhythmias in the vulnerable population of cardiovascular patients.

Acetaminophen is available in both intravenous and oral formulations and is an effective analgesic agent for mild pain or as an adjunct in multimodal pain control, via activation of the descending serotonergic inhibitory pathways within the central

nervous system. Studies have demonstrated that IV acetaminophen can decrease the total dose of morphine required by patients post-operatively [30]. Immediately after surgery, patients will benefit from scheduled dosing (every 6–8 h), not exceeding 3000 mg daily. With its relatively benign side effect profile, acetaminophen supplementation is a useful adjunctive agent in individuals with cardiovascular disease.

Additionally, neuropathic pain medications are a mainstay in multimodal pain control and can be particularly helpful in patients with heart disease, given the common comorbid conditions, such as diabetes (addressed below in *Inpatient treatment for pain conditions specific to cardiovascular disease*).

6.5.2 *Scenario 2: Management of Multiple Fractures in the Emergency Department Following a Motor Vehicle Accident*

In addition to stabilization of life-threatening processes, adequate analgesia is essential to avoid adverse cardiac events in those individuals with pre-existing heart disease. Inadequate analgesia coupled with the stress response of acute injury can lead to an adverse hemodynamic response (tachycardia, hypertension, or vasoconstriction), increased catabolism, an impaired immunity, and hemostatic derangement including platelet activation alterations. Attenuation of this response can decrease mortality and enhance patients' quality of life [31]. In patients with ischemic heart disease, pain control leads to a reduction in sympathetic tone, lowering heart rate and increasing vasodilation, which leads to a more favorable oxygen-supply ratio. In the acute setting, this is achieved most rapidly with intravenous opioids such as fentanyl or hydromorphone. However, patients should be closely monitored for hypoventilation, leading to hypercarbia and acidosis, as these processes have detrimental implications in the setting heart failure (addressed below in *Management of pain in the inpatient setting*).

As noted above, supplementation with ketamine and scheduled acetaminophen can enhance analgesia while minimizing opioid requirements and thus, their undesired side effects. Regional techniques can provide a helpful adjunctive therapy via either neuraxial analgesia or peripheral nerve blockade. For extremity fractures, peripheral nerves are directly targeted with long-acting local anesthetics (such as bupivacaine or ropivacaine) via single shot or continuous infusion with an indwelling catheter.

If traumatic rib fractures are present, analgesia is vital not only to avoid hemodynamic volatility, but also to avoid significant respiratory compromise. The development of pneumonia is the most common complication of rib fractures, significantly contributing to mortality. Patients will minimize their tidal volume and coughing effort to reduce chest wall motion and associated pain. Pain control is thus imperative to allow patients to tolerate deep breathing and coughing, improving lung volumes, preventing alveolar collapse, and clearing secretions.

Epidural catheters allow for continuous local anesthetic and opioid infusion, providing targeted pain control and decreasing the incidence of nosocomial pneumonia [32]. Specifically in patients with ischemic cardiac disease, epidural analgesia can improve coronary function and myocardial oxygen balance, reducing the number and duration of ischemic episodes during an acute stress period [33]. When epidural placement is contraindicated, such as in patients on either antiplatelet or anticoagulation agents, a paravertebral catheter can be placed to provide a continuous infusion of local anesthetic to one side of the thorax. Epidural infusions may have detrimental hemodynamic effects in the setting of heart failure and should be used with caution. Additionally, local anesthetic agents all possess pro-arrhythmic potential and should be used carefully in patients with a pre-existing history of cardiac dysrhythmias (addressed below in *Management of pain in the inpatient setting*).

6.5.3 Inpatient Treatment for Pain Conditions Specific to Cardiovascular Disease

Effective pain management in the context of cardiac disease is vital to avoid undue stress and hemodynamic volatility. Pain states specific to cardiac disease include chronic chest pain, claudication secondary to associated peripheral vascular disease, and neuropathic pain from peripheral edema or concomitant chronic diabetes. Modalities specific to these pain states are discussed below.

6.5.3.1 Chronic Chest Pain

Refractory angina pectoris is defined as the presence of angina due to coronary insufficiency in the setting of coronary artery disease despite optimal medical, surgical or percutaneous therapy. When first approaching pain management in this specific population, it is essential to ensure they are taking optimal medical therapy and have undergone all possible revascularization therapies. If their chronic chest pain persists, the first line should be acetaminophen. Additionally, opioids can be considered, but the risks of addiction or hypoventilation should be weighed against their benefit. Other potential inpatient interventions include use of a TENS unit or temporary relief via a left-sided stellate ganglion block.

The TENS unit works via high-frequency stimulation of large nociceptive myelinated type A fibers, which inhibits impulses through smaller, unmyelinated type C fibers, reducing the activation of central pain receptors. One electrode is placed within the dermatome with the highest pain intensity and the other on the contralateral dermatome. Previous studies have demonstrated that use of a TENS unit can decrease anginal symptoms and nitrate use. Decreasing the pain stimulus can lead to a reduction in sympathetic discharge that leads to decreased cardiac work load and decreased myocardial oxygen demand [34].

The sympathetic autonomic nervous system relays anginal symptoms from the myocardium to the central nervous system via release of excitatory substances such as adenosine or bradykinin. The stellate ganglion block works as a sympathectomy via interruption of this pathway [35]. A local anesthetic is infiltrated around the cervical plexus under ultrasound guidance, generally via a paravertebral approach. Studies have demonstrated that patients can have relief beyond the period of action of the local anesthetic via the reversal of the cellular mechanisms responsible for a hyperalgesic state [36].

6.5.3.2 Claudication Pain

Peripheral artery disease (PAD) is common among patients with cardiovascular disease as the systemic disease process of atherosclerosis that affects coronary arteries also damages the peripheral vasculature. Claudication is defined as reproducible discomfort for a particular muscle group, caused by exercise and improved with rest. Just as coronary artery disease manifests as chest pain, claudication is secondary to an imbalance between supply and demand for blood flow due to peripheral artery disease. Within the inpatient realm and upon discharge, treatment of claudication pain can facilitate greater mobility and ability to rehabilitate. Although claudication pain infers an increased cardiovascular risk, in most cases it has a low risk of progression to limb-threatening ischemia [37]. Like coronary artery disease, the first line treatment should always target the underlying disease process with risk factor modification (especially smoking cessation), exercise, and optimal medical therapy. In patients where no procedural intervention is warranted (those without threat of critical limb ischemia), the only agent available in the US shown to provide consistent pain relief with ambulation is cilostazol. The medication works as an analgesic via suppression of platelet aggregation and direct arterial vasodilation. Cilostazol can be started in the inpatient setting, but achieves its full benefit 4 weeks after initiation. It should be noted that this medication is contraindicated in patients with advanced heart failure as other phosphodiesterase inhibitors have been shown to increase mortality in this population [38].

6.5.3.3 Neuropathic Pain

Neuropathic pain is commonly encountered in patients with cardiovascular disease, due to either concomitant diabetes, chronic nerve compression secondary to peripheral edema, or via other etiology. The first line analgesic therapies include antidepressants (Selective Norepinephrine Reuptake Inhibitors (SNRIs), Tricyclic antidepressants (TCAs) and calcium channel ligands (gabapentin, pregabalin).

The use of antidepressant agents for neuropathic pain carries both the benefit of analgesia as well as the relief of associated depressive symptoms. The analgesic mechanism remains unknown but may be related to action on serotonin and norepinephrine reuptake inhibition [39]. Additionally, there is some evidence they may

potentiate the endogenous opioid system [40]. The main SNRI agents studied and approved in the treatment of neuropathic pain are duloxetine and venlafaxine. Venlafaxine can be used both in acute and chronic pain conditions, making it useful for inpatient treatment. However, it should be used with caution in those with cardiac disease as it has a propensity towards cardiac conduction abnormalities and increased blood pressure. The most commonly used and most widely studied TCA in neuropathic pain is amitriptyline, though other agents (doxepin, imipramine, nortriptyline and desipramine) can be used with success. The dosing required for analgesic effect is typically lower than that required for anti-depressive effect. Effect may be experienced in as soon as 1 week, but may take up to 6–8 weeks for maximal analgesia [41]. Like SNRIs, TCAs have the potential for conduction disturbances including increased intraventricular conduction, prolongation of the QT interval, and prolongation of conduction through the atrioventricular node. As such, prior to initiation, patients should have a baseline ECG performed. TCAs should be avoided in individuals with severe cardiac disease and those with pre-existing conduction disturbances.

Pregabalin and gabapentin belong to the class of calcium channel alpha 2-delta ligands. They exert their effect by binding to the voltage-gated calcium channels at the alpha 2-delta subunit, inhibiting neurotransmitter release. Gabapentin should be initiated at a low dose with a gradual increase until desired effect, with a maximum dose of 3600 mg daily, in three divided doses [41]. Pregabalin is a lipophilic gamma aminobutyric acid (GABA) analog, which diffuses across the blood-brain barrier more effectively than gabapentin, and thus, may provide faster analgesia [42]. Both agents can produce dose-dependent dizziness and sedation. In older patients, respiratory depression has been reported, especially when individuals are receiving other analgesic agents or sedatives [43].

6.6 Pain Assessment Tools

Generalized pain assessment tools can be used within the cardiovascular patient population, including either a numeric rating scale or a verbal rating scale. In critically ill patients who may not be able to communicate, validated pain assessment tools include the Behavioral Pain Scale (BPS) or the Critical Care Pain Observation Tool (CPOT), which use metrics such as facial expression, body movement, and compliance with mechanical ventilation as surrogates for pain [44].

6.7 Challenges in Management of Pain While in the Hospital

Inpatient treatment of pain, specifically within patients with cardiovascular disease, carries several challenges including their increased risk of hemodynamic instability, arrhythmogenic propensity, cardiac sensitivity to hypoventilation and

hypercarbia, and ensuring pain control is not masking intervenable cardiac disease. Specific medications to use with caution in this patient population are addressed below.

6.8 Management of Pain in the Inpatient Setting

6.8.1 Modalities and Medications to Use with Caution in Heart Failure and Coronary Artery Disease

6.8.1.1 Ketamine

Ketamine is a commonly used analgesic agent, which acts by blocking *N*-methyl-D-aspartate (NMDA) receptors, reducing glutamate release, and by binding to sigma-opioid receptors [26]. Ketamine is used to reduce opioid consumption in post-surgical patients, hyperalgesia, and neuropathic pain. In addition to its opioid-sparing properties, ketamine can be a beneficial analgesic agent given its lack of significant respiratory depression and maintenance of airway reflexes. Ketamine's effect on the cardiovascular system is primarily that of a sympathomimetic in an intact automatic nervous system, increasing blood pressure, heart rate, and cardiac output. Administration of ketamine can lead to increased levels of epinephrine and norepinephrine within 2 min of administration [45]. Although these effects are generally desirable in the critically ill, abrupt increases in heart rate and blood pressure may detrimentally unbalance myocardial oxygen supply and demand in patients with coronary artery disease.

In the absence of an intact autonomic nervous system and catecholamine depletion, as seen in decompensated heart failure, ketamine acts as a direct myocardial depressant. Studies that isolate the direct effects of the drug have demonstrated up to a 40% decrease in cardiac output [46]. In summary, ketamine may be a helpful analgesic agent given its stable hemodynamic profile, but may precipitate hemodynamic decline in individuals with a depleted catecholamine reserve.

6.8.1.2 Opiates

Opioid medications should be used with caution in the setting of heart failure, especially right-sided heart failure and associated pulmonary hypertension. Opioid-induced oversedation can lead to hypoventilation and subsequent carbon dioxide retention. Hypercarbia and acidosis acutely increase pulmonary vascular resistance, exacerbating right ventricular dysfunction, and leading to hemodynamic compromise [47]. Additionally, high levels of CO2 (80–90 mmHg) directly reduce cardiac output, blood pressure, and heart rate [48]. In patients with decompensated heart failure, known right-sided disease, or pulmonary hypertension, opioids should be administered in small doses and titrated gradually to avoid oversedation.

6.8.1.3 Pregabalin

Pregabalin is a frequently encountered medication in patients with cardiac disease. Multiple randomized control trials have shown the benefits of using pregabalin for the treatment of neuropathic pain, and thus it is one of the first line therapies. Pregabalin is efficacious and also has the advantage of being easily titratable, tolerated well, and has few interactions with other medications. Dizziness, somnolence, and peripheral edema are some of the most common side effects that have been reported [49]. However, this medication should be used with caution in patients with decompensated heart failure. There have been numerous case reports of heart failure exacerbations in patients after the initiation of pregabalin [49–52]. These case reports have shown subsequent resolution of edema after discontinuation of this medication. While there is not necessarily overwhelming data to support completely avoiding this medication in heart failure patients, there appears to be a potential risk for a dose dependent increase in both peripheral and central edema [49, 52, 53]. The incidence of peripheral edema in patients taking pregabalin in clinically controlled trials was found to be 6%, compared to 2% in the placebo group. While data in heart failure patients is not robust, the FDA has recommended that pregabalin be used with caution in patients with New York Heart Association (NYHA) class III and IV heart failure. Furthermore, the FDA has recommended that pregabalin be used with caution in patients already taking thiazolidinedione, as it may exacerbate heart failure symptoms. Both pregabalin and thiazolidinedione antagonize L-type calcium channels and are thought to be involved in peripheral vasodilation and interstitial fluid accumulation [52, 54]. In patients who exhibit either peripheral or central edema, but have experienced relief with pregabalin, a consultant physician should consider utilizing other analgesic options.

6.8.1.4 SNRIs

Venlafaxine is another medication that should be used with caution in patients with cardiac disease. Venlafaxine is an SNRI that is commonly prescribed to patients with depression, anxiety, fibromyalgia, neuropathic pain, and chronic musculoskeletal pain. Increased levels of norepinephrine leading to elevated heart rate and blood pressure have been implicated in some of the adverse cardiac events related to this medication [55, 56]. There have been multiple case reports of heart failure exacerbations associated with high doses of venlafaxine or venlafaxine taken in combination with other SNRIs (i.e., Duloxetine) [55, 57–59]. These patients were previously hemodynamically stable with some experiencing subsequent resolution in symptoms after discontinuation of the medication. Higher doses of venlafaxine (300 mg/day) have also been found to be associated with clinically significant QTc prolongation, hypertension, and orthostatic hypotension [60, 61]. Lastly, venlafaxine should be used with caution in patients with coronary artery disease. There has been a case report of this medication possibly inducing an acute ischemic event in a patient with previously mild stable angina [62]. While this medication certainly has benefits for

treating both chronic musculoskeletal and neuropathic pain, it should be titrated cautiously in patient with underlying cardiac disease. Particular attention should be paid to patients already taking an SNRI as well as patient who may have altered metabolism of this medication (i.e., CYP2D6 genetic polymorphism) [59]. As a consultant physician, one should monitor for signs and symptoms of heart failure and consider obtaining an EKG to assess for both QTc prolongation and ischemia when starting this medication.

Duloxetine is another SNRI that is used frequently to treat both acute and chronic pain. While duloxetine has been shown to cause a mild increase in blood pressure, it does not appear to be associated with any significant cardiovascular risk [63]. In animal models, duloxetine has been shown not to significantly affect smooth or cardiac muscle function. There also does not appear to be any arrhythmogenic risk associated with the medication [64].

6.8.1.5 Non-steroidal Anti-inflammatory Drugs (NSAIDs)

The use of non-steroidal anti-inflammatories is associated with an increased risk of adverse cardiovascular events, including heart failure, myocardial infarction, atrial fibrillation, and cardiovascular death. This effect is related to the medications' inhibition of cyclooxygenase (COX)-2, leading to reduced prostaglandin I2 production by the vascular endothelium coupled with a lack of inhibition of the potentially prothrombotic platelet thromboxane A2 production [65]. This relative reduction in prostacyclin activity predisposes the endothelium to injury and subsequent poor cardiovascular outcomes [66]. In the setting of cardiovascular disease, other analgesic agents are preferred due to this population's relatively high baseline risk.

6.8.1.6 Neuraxial Analgesia

Although neuraxial analgesia is a useful opioid-sparing technique, epidural anesthesia has potential for detrimental effect in tenuous heart failure. In addition to their desired sensory blockade, local anesthetic agents in the epidural space also create a motor and sympathetic blockade. This sympathectomy increases venous capacitance and leads to peripheral redistribution of blood, decreasing venous return to the heart, reducing preload. This acute reduction in preload, cardiac output, and systemic perfusion pressure can have an adverse effect on both left and right ventricular perfusion and function. Blockade of the cardiac sympathetic nerves (T1-T5) by cervicothoracic epidural levels can directly decrease contractility as well as adversely disrupt the baroreceptor reflex. Left ventricular contractility can be reduced up to 40–50%. Although this is generally tolerated in individuals with normal cardiac function, this diminution can have life-threatening implications in those with limited cardiac reserve. The baroreceptor reflex is responsible for regulation of heart rate, contractility, and peripheral resistance in response to changes in blood pressure. Cardiac fiber sympathectomy and attenuation of this reflex can lead to

life-threatening paradoxical bradycardia in hypotensive patients undergoing epidural anesthesia. Although not contraindicated in the setting of heart failure, providers should proceed with caution as epidural analgesia may significantly diminish the capacity of the heart to respond to hemodynamic challenges in individuals with limited reserve secondary to heart failure [33].

6.8.2 Medications to Use with Caution in Pre-existing Arrhythmias

In patients with pre-existing arrhythmias, there are several medication classes that should be used with caution, given their propensity to both exacerbate pre-existing arrhythmias and initiate new dysrhythmias. These include methadone, sodium channel blockers/local anesthetics, and alpha-2 agonists.

6.8.2.1 Methadone

Methadone is a synthetic opioid used in opioid addiction, chronic pain, and the perioperative setting. Methadone has many beneficial properties including excellent oral bioavailability, effectiveness, low cost, long half-life and availability in oral, parenteral, and suppository forms. Methadone exerts its effect via agonism of the mu-opiate receptor, both centrally and peripherally, leading to analgesia and euphoria. Unique among opioids, the drug also antagonizes *N*-methyl-D-aspartate receptors increasing its analgesic effect [67].

Some of methadone's unique safety concerns stem from the drug's long and variable half-life, which ranges between 15 and 55 h. Methadone is metabolized both by the liver and via intestinal CYP3A4 (and to a lesser extent, via CYP2D6). Significant inter-patient variability in enzyme activity contributes to large differences in the clearance and half-life of the drug [68]. Additionally, methadone is highly bound to plasma proteins (specifically α_1-acid glycoproteins), which can be affected by certain disease states such as cancer, as well as lead to multiple drug-drug interactions [67]. The inherent unpredictability of methadone is pertinent both for its desired effect but also side effect profile. Specific to the cardiovascular system, methadone has a propensity for QTc interval prolongation, predisposing patients to dangerous ventricular arrhythmias such as torsades de pointes (TdP) [69]. From 2000 to 2011, methadone was the second most common offender in QTc prolongation and TdP, behind dofetilide [70].

Methadone should be used with caution in patients with pre-existing arrhythmias and ECG abnormalities, including baseline QT prolongation (>450 ms) or T-wave lability, sinus bradycardia, heart block, or incomplete heart block with pauses or premature complexes. Additionally, patients with structural heart disease, including heart failure, a history of myocardial infarction, or left ventricular hypertrophy are at increased risk of methadone-induced TdP.

The normal QTc in adults is 420 ± 20 ms. The risk of TdP increases with greater prolongation of the QTc interval, primarily occurring in patients with QTc intervals >500 ms, though risk is increased starting at QTc intervals of 450 ms [71]. Virtually every medication that prolongs the QTc interval, including methadone, acts by blocking the outward IKr current (delayed rectifier potassium current, also known as hERG channel), which is crucial for the repolarization of cardiac action potentials, leading to an increased action potential duration, and QT interval prolongation [72]. Prolongation of the ventricular repolarization can lead to oscillation of the membrane potential referred to as early after depolarization (EAD). If EAD reaches a critical threshold in a large area of myocardium, it can precipitate an ectopic beat, inducing reentrant excitation, and subsequent TdP, marked by progressive, sinusoidal, and cyclic alteration of the QRS [73]. The ventricular dysrhythmia is generally short-lived and terminates spontaneously. However, it has the potential to lead to ventricular fibrillation and result in cardiac arrest [74].

A lower heart rate (as seen in sinus bradycardia, heart block, or incomplete heart block with pauses or premature complexes) results in less potassium moving out of the cell during repolarization, as there are simply fewer repolarizations. This reduction in extracellular potassium concentration enhances the degree of drug-induced inhibition of IKr, increasing the QTc interval [75].

Given the above risk, the American Pain Society, in conjunction with the Heart Rhythm Society created a consensus statement and guidelines for prescribing methadone, which includes obtaining a baseline EKG prior to initiating treatment and avoiding use in patients with a baseline QTc >500 ms. [69] Methadone can be an effective opiate option both in the outpatient, inpatient, and the perioperative realm. However, careful attention must be paid its pro-arrhythmic potential and optimization of patient risk factors, including electrolyte disarray (such as hypokalemia or hypomagnesemia), baseline heart rate and QTc interval, and potential drug-drug interactions.

6.8.2.2 Local Anesthetics

Sodium channel blockers, also known as local anesthetics, are widely used within the inpatient population via a wide array of delivery routes including intravenous, subcutaneous, epidural, intrathecal, or direct infusion to the peripheral nerve. When infused around either the peripheral or central nervous system, the local anesthetic agent works via binding the α subunit of the sodium channel, rendering it inactive. If the sodium molecule cannot traverse the membrane, the cell cannot depolarize, and no action potential is created, leading to the desired clinical effect of numbness [48]. Systemic lidocaine (via intravenous route) is used in both acute and chronic pain. Specifically, in neuropathic pain, systemic lidocaine is believed to work by attenuation of peripheral nociceptor sensitization and central hyperexcitability via its sodium channel blocking action. Additionally, IV lidocaine has potent anti-inflammatory properties, decreasing circulating cytokines, which contributes to its analgesic properties [28]. However, local anesthetics carry the risk of dysrhythmias,

especially in the setting of LAST (Local Anesthetic Systemic Toxicity). Although they are not contraindicated in the setting of a patient history of arrhythmias, associated conditions such as extremes of age and structural cardiac disease make this patient population susceptible.

Factors that contribute to the toxicity and propensity for arrhythmias of local anesthetic agents include the site and route injection, specific drug, dose used, co-administration of vasoconstricting agents, and drug metabolism. In terms of the injection site, highly vascular areas are at the greatest risk for uptake. Careful attention to the maximum dose of the various local anesthetic agents should be paid in order to avoid exacerbating pre-existing arrhythmias or cardiotoxicity. The addition of vasoconstricting agents lowers the peak blood level while increasing the time to achieve peak serum level, effectively decreasing the risk of toxicity [48].

The cardiovascular effects of systemic local anesthetic levels are multifactorial and complex. Their blockage of sodium, calcium, and potassium channels can lead to conduction disturbances, impaired contractility, and loss of vascular tone [76]. The above effects are dose-dependent and proportional to the potency of the agents used. Within the myocardial tissue, blockage of the sodium channels in the fast-conducting tissues of the purkinje fibers and ventricles decreases the rate of repolarization, effective refractory period, and action potential, leading to prolongation of the PR interval and widening of the QRS complex. At toxic drug levels, local anesthetic's effect on myocardium may induce arrhythmias, heart block, ventricular contractile depression, hypotension, or complete cardiovascular collapse [48].

Of the available local anesthetic agents, bupivacaine has the highest risk of cardiac toxicity, due to its strong affinity for resting or inactivated sodium channels and slow dissociation from myocardial sodium channels during diastole. Studies have repeatedly demonstrated that bupivacaine is associated with more pronounced changes in conduction and greater risk of terminal arrhythmias. Intravenous injection of bupivacaine can lead to left ventricular depression, heart block, ventricular tachycardia or ventricular fibrillation. Bupivacaine's propensity for cardiogenic toxicity comes from its chirality. Along with mepivacaine and ropivacaine, bupivacaine has chiral carbons, which can exist as one of two optical isomers. The R+ isomer of bupivacaine blocks more strongly and dissociates more slowly from cardiac sodium channels than its S-counterpart [77]. Conversely, ropivacaine, derived from mepivacaine is produced as the S-enantiomer only, with a presumed decrease in cardiovascular toxicity [78].

Careful monitoring when administering local anesthetics and knowledge of the signs and symptoms of LAST can lead to prompt treatment and avoidance of severe cardiac toxicity. Patients should be monitored with non-invasive blood pressure measurements, electrocardiography, and pulse-oximetry at a minimum. Prodromal symptoms of impending neurologic or cardiac collapse may include lightheadedness, dizziness, blurred vision, tinnitus, or perioral numbness. These symptoms can quickly lead to loss of consciousness, seizures, myocardial depression, ventricular tachycardia, ventricular fibrillation, or pulseless electrical activity [79].

Local anesthetic use is not contraindicated for those with pre-existing arrhythmias, and may be a helpful alternative to those in which systemic sedating agents

must be avoided. However, those with structural heart disease or pre-existing arrhythmias are at a higher risk for the cardiotoxicity. As such, caution and careful monitoring should be practiced within this patient population.

6.8.2.3 Alpha-2 Agonists

Commonly used alpha-2 agonists used in the inpatient realm include clonidine and dexmedetomidine. Both agents exert their analgesic properties via their actions on the alpha-2 postsynaptic receptors within the dorsal horn of the spinal cord, peripheral nerves, and locus coeruleus, inhibiting the release of norepinephrine and thus terminating the propagation of pain signals. When used for its analgesic properties, clonidine is added as an adjunct to local anesthetics within either an epidural infusion or spinal injection. Dexmedetomidine is most commonly delivered as an infusion, primarily for sedation, but is emerging as an effective analgesic agent.

Alpha-2 agonists possess significant anti-hypertensive and negative chronotropic effects, leading to hypotension, bradycardia, and varying degrees of heart block. These effects are seen due to inhibition of central sympathetic outflow, leading to a decreased release of norepinephrine and epinephrine [48].

Dexmedetomidine, which has an eightfold greater selectivity for the alpha-2 receptor over clonidine, has been shown to cause a dose-dependent decrease in blood pressure and heart rate. When used with caution, it can be useful analgesic agent for those with heart disease, given its sympatholytic properties and ability to provide both analgesia and anesthesia without appreciable respiratory depression. The drug will predictably cause a biphasic blood pressure response, with an initial hypertension, followed by a sustained decrease. The observed bradycardia is caused by a combination of baroreflex activation, a centrally mediated reduction in sympathetic tone, and increased vagal tone. Severe bradycardia is a well-documented side effect of dexmedetomidine, with some case reports citing asystole with administration in susceptible patients [80]. Both clonidine and dexmedetomidine should be avoided in those with pre-existing bradycardia, an advanced heart block, or a fixed stroke volume.

6.9 Discharge Plan for Pain Management

As the cardiac patient transitions from the inpatient setting to the outpatient setting, they must undergo changes in their treatment plan. Some medications started while the patient is in the hospital will be continued, while others that are used to treat the acute phase of their pain will be tapered off and discontinued. Neuraxial, intravenous, and regional modalities are no longer available to be employed after the patient has been discharged and a plan must be put in place to make sure the patient has their pain adequately controlled. For this reason, it is of the utmost importance to transition patients to a stable oral regimen leading up to their discharge from the

hospital. In the cardiac patient, acetaminophen is an important, non-opiate medication that should be utilized in those who do not have a contraindication to this medication [21]. Up to 4000 mg per day may be used and should be scheduled and spaced accordingly throughout the day in divided doses to provide baseline analgesia as patients transition from the inpatient setting. For patients who have recently undergone a procedure, suffered a trauma or other inciting event that can cause an acute pain flare, short acting oral opiate medication should be utilized and titrated overtime to provide additional analgesia on top of acetaminophen. As times passes, it is important to eventually wean these medications or transition to more long-acting opiate medications if needed. Adjunctive medications such as tricyclic antidepressants, SNRIs, and anticonvulsants can also be added to manage both neuropathic and chronic pain [2]. The benefit of starting these medications in the inpatient setting and continuing them in the outpatient setting, is that they frequently take weeks to months to see their analgesic effects. These medications should be titrated accordingly over time as long as patients tolerate their associated side-effects. Muscle relaxers can also be added to a patient's medication regimen to help with musculoskeletal spasticity and pain. Most muscle relaxers are safe to use in patients with cardiac disease with the exception of cyclobenzaprine. Cyclobenzaprine is contraindicated in patients with arrhythmias, congestive heart failure, and recent myocardial infarctions [81]. Topical analgesics such as transdermal lidocaine may also provide additional benefit. Aqua therapy, physical therapy, and alternative medicine/complementary therapies are important components to a balanced outpatient pain regimen. Furthermore, for certain patient populations, psychological assessment and therapy may also be beneficial. While NASIDs are commonly utilized in managing pain after leaving the hospital, they should be avoided in patients suffering from heart failure and coronary artery disease [21]. Lastly, for patients that are especially difficult to treat, consider placing a referral to an outpatient pain medicine specialist to help in the transition process from the inpatient to the outpatient setting.

6.10 Summary

- Multimodal pain control can help minimize side effects while providing adequate pain control. In the patient with cardiovascular disease, the multimodal armamentarium includes opioids, acetaminophen, ketamine, neuropathic pain medications (anti-depressants, calcium-channel ligands), as well as regional anesthesia.
- Pain states specific to cardiovascular disease include chronic chest pain, claudication pain, and neuropathic pain.
  - Patients with chronic chest pain related to coronary artery disease (CAD), despite interventional and optimal cardiovascular medical therapy can be treated with opiates, acetaminophen, use of a TENS unit, or a stellate ganglion block.

  - Peripheral artery disease (PAD) is common among patients with cardiovascular disease as the systemic disease process of atherosclerosis that affects coronary arteries also damages the peripheral vasculature. The first line medication for claudication pain in the setting of PAD is cilostazol.
  - Neuropathic pain is commonly encountered in patients with cardiovascular disease, due to either concomitant diabetes, chronic nerve compression secondary to peripheral edema, or via other etiology. The first line analgesic therapies include antidepressants (SNRI's, TCA's) and calcium channel ligands (gabapentin, pregabalin), however one may need to exercise caution in the case of documented arrythmias or severe heart failure.

- Ketamine can be a useful analgesic agent given its potent NMDA-receptor antagonism, hemodynamic stability, and lack of significant respiratory depression. However, in the absence of an intact autonomic nervous system and catecholamine depletion, as seen in decompensated heart failure, ketamine acts as a direct myocardial depressant.
- NSAIDs should be avoided in patients with coronary artery disease and their use is associated with an increased risk of adverse cardiovascular events, including heart failure, myocardial infarction, atrial fibrillation, and cardiovascular death.
- Medications that should be used with caution in patients with pre-existing arrhythmias include methadone, sodium channel blockers/local anesthetics, and alpha-2 agonists.

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Chapter 7
Patient with Heart Transplant

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7.1 Introduction

Heart transplant has become the standard of care for patients with end-stage heart failure (Fig. 7.1). Some of the common indications and contraindications for heart transplant are listed below (Table 7.1):

As per United Network for Organ Sharing (UNOS), of all transplants performed since 1988, 9.5% are heart transplants. More than 5000 heart transplants are performed per year worldwide.

In 2018, approximately 3408 heart transplants were performed in the US alone. Previously, long term survival of allograft was limited. With improvement in transplant management, survival of recipients has improved significantly over the past several years. Along with improved medical management of recipients, focus has also shifted towards improving Quality of life (QOL) of the survivors. Nowadays, it is not uncommon in medical practice to come across patients with primary, multiorgan or repeat transplants experiencing chronic pain resulting in low QOL or loss of jobs because of the development of debilitating pain after transplant.

In the immediate postoperative period, acute postoperative pain could be present at rest and with activities like coughing and walking, but it improves in intensity after the initial 24 h. Pain can persist for days or weeks after the initial surgical insult and if not managed appropriately in the immediate postoperative period, it could lead to chronic pain syndromes. Inadequate pain management in the immediate postopera-

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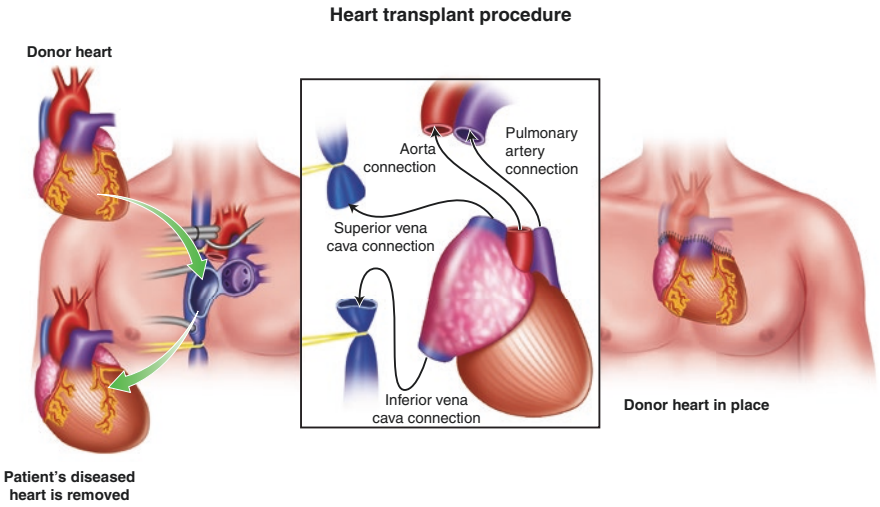

Fig. 7.1 Heart transplant procedure

Table 7.1 Heart transplant [1]

Indication	Contraindication
1. LVEF <35% or severe heart failure with severe functional limitation or symptoms refractory to medical or device managementNYHA Class IIIb-IV 2. Refractory Cardiogenic Shock 3. Acute MI or Myocarditis 4. Ischemic Heart disease refractory to medical management or patient is not a candidate for surgical or percutaneous revascularization 5. Refractory arrhythmias 6. Severe hypertrophic or restrictive cardiomyopathy 7. Congenital heart disease without Pulmonary hypertension 8. Non-metastatic cardiac tumor	1. Metastatic Malignancy 2. Refractory Pulmonary Hypertension 3. Active HIV or Hep C 4. Poorly controlled Diabetes with end organ damage 5. Renal failure 6. End stage Liver ds 7. Severe Peripheral Vascular ds refractory to intervention 8. Active substance abuse 9. Non-compliance 10. Lack of support system 11. BMI > 35 kg/m^2 12. Mental Retardation

tive period has been identified to result in increased postoperative morbidity, poor quality of life and functional capacity, prolonged use of opioids and increased health care costs [2]. Chronic pain after cardiac surgery is under identified and undertreated. Incidence of chronic pain after cardiac surgery is reported to be between 21 and 55% [3]. There are conflicting results of various studies that tried to identify risk factors for development of chronic pain after cardiac surgery. Some studies identify gender, prolonged surgeries lasting for more than 3 h, ASA grade III or above, younger patients, obesity, preoperative anxiety and pain levels as independent factors for development of chronic postoperative pain (CPOP) and some do not [3–5].

Post cardiac surgery, pain may be somatic, visceral or neurogenic in nature, and acute or chronic in duration. Understanding pathophysiological changes related to surgery, anesthesia and extracorporeal circulation is important to improve patient comfort in the immediate and late postoperative periods. Inadequate pain management during major cardiac surgery could prolong the course of illness and result in inadequate tissue healing, immunosuppression, infection and development of chronic postoperative pain.

7.2 Pathophysiology

Pain after surgical incision is identified as a different entity as compared to other acute or chronic pain conditions. Acute postoperative pain is a combination of surgical insult to the tissues resulting in a surgical wound and activation of endocrine, inflammatory, autonomic and sensory signaling cascades in the central and peripheral sites. Incisional pain is planned and inflicted under controlled conditions. It results in unfortunate consequences due to modulation of neuronal "plasticity" that can result in chronic pain. There is active research to better understand animal pain models, pain mechanism in postoperative period in patients, behavioral changes in animal models related to pain induced by incision in order to minimize procedural pain [6, 7]. Painless procedures can prevent dysregulation of multiple systems induced by acute surgical pain, development of chronic pain and multiorgan dysfunction in the long term.

Acute postoperative pain has been classified as "Clinical Pain" or "Receptor Pain" depending on the innocuous stimulation of the tissues by incision or irritation of nociceptors [8, 9]. Clinical pain can last longer than expected after being incited by the noxious stimulus. It is diffuse and difficult to locate and patient's report aggravation of pain on movement. Clinical pain results from induction of sensitization mechanism after trauma to the tissue and has slow speed of conduction. Receptor pain, similarly to physiological pain, is initiated by irritation of peripheral nociceptors. Once peripheral Aδ and C fibers are stimulated by noxious stimuli, the impulse is transduced up the ladder from posterior roots or ganglia of the cranial nerves (V, VII, IX, and X) and dorsal horn of the spinal cord to reach the cerebral cortex and limbic system where perception of pain occurs. The electrical impulse generated in peripheral receptors is transduced via lateral and medial spinohypothalamic, spinomesencephalic, and spinoreticular pathways to the thalamus, reticular formation, pons, hypothalamus, and periaqueductal gray matter to cerebral cortex and limbic system. Intensity of generated impulse is modulated by endogenous neurotransmitters (noradrenergic, cholinergic, serotonergic, and GABA-ergic systems) and opioids. They modify the intensity of pain perceived in cerebral cortex by either enhancing or inhibiting the transmission of the noxious stimulus.

7.2.1 Activation of Inflammatory Cascade

Injury to tissue results in activation of the inflammatory cascade in order to initiate healing and cope with injury. Several mediators like substance P, serotonin, histamine, cytokines, and leukotrienes are released from inflammatory cells. Noxious

stimuli can also cause cellular changes resulting in pH alteration and influencing membrane permeability leading to vasodilation, swelling and inflammation [10]. These mediators play a significant role in peripheral sensitization by stimulating primary afferent nerves and activation of redundant nociceptors. Peripheral activation by inflammatory mediators bring about changes in CNS resulting in central sensitization [11, 12]. If not attended appropriately this progresses to development of primary or secondary hyperalgesia, allodynia or other regional pain syndromes.

7.2.2 Activation of the Sympathetic System

Activation of the sympathetic system in response to pain via adrenergic mediators adversely affects multiple organ systems in the body. Tachycardia, hypertension, increased peripheral arterial tone resulting in decreased organ perfusion, impaired gastrointestinal motility, sphincter spasms resulting in colics and urinary retention are some of the adverse effects of acute postoperative pain resulting in increased postoperative morbidity and mortality. Malberg et al., reported significant alterations in the sympathetic and vagal balance in the early postoperative period after cardiac surgery. In their study, they reported normal functioning of sympathetic tone and depressed vagal tone for 20 h in the postoperative period and identified this imbalance as a cause of high incidence of atrial tachycardia in the early postoperative period after cardiac surgery [13].

7.2.3 Activation of Endocrine Super Systems

Prolonged stimulation of the sympathoadrenal-hypothalamo-pitutary super systems by inadequate postoperative management of acute pain could result in dysregulation of homeostasis of the body. Leading to suppression of the immune system, poor wound healing and chronic pain syndromes [14, 15]. Decreased levels of insulin and increased circulating levels of cortisol, catecholamine, antidiuretic hormone, corticotropic hormone, renin, angiotensin, and aldosterone is seen in response to nociceptive stimulation that causes activation of sympathoadrenal-hypothalamo-pitutary super systems [11].

7.2.4 Autonomic Innervation of Heart

7.2.4.1 Sympathetic Architecture

The inferior-middle cervical stellate paravertebral ganglion contains cell bodies of postganglionic sympathetic fibers. These sympathetic nerves innervate atrial and ventricular myocytes modulating inotropy and lusitropy of heart. The principle

neurotransmitter at these nerve terminals is norepinephrine. Neuropeptide Y (NPY) and galanin have been identified as co-transmitter at these sympathetic terminals [16].

7.2.4.2 Parasympathetic Architecture

Parasympathetic innervation of heart primarily modulates heart rate by modulating hyperpolarization of both sino-atrial and atrio-ventricular nodal tissue. Primary neurotransmitter released in cardiac ganglion is acetylcholine. Vasoactive intestinal peptides (VIP) and Nitric Oxide (NO) act as co transmitters at these terminals [17, 18]. Cardiac ganglion receives preganglionic parasympathetic inputs from Vagus. These ganglions are found embedded in atrial epicardial fat, plexus along the walls of major vessels and within ventricular walls [19].

7.2.4.3 Transplanted Heart Physiology

Heart transplant recipients have altered cardiovascular control and are unable to feel pain due to cardiac ischemia due to loss of inflow and outflow of afferent and efferent nerve signals [20]. The surgically dissected transplanted heart is extrinsically denervated due to the disruption of parasympathetic vagal neurons and intrinsic postganglionic sympathetic nerve fibers traveling from the stellate ganglia to the myocardium [21]. Cardiac denervation results in higher resting heart rate due to the absence of parasympathetic vagal input and show loss of normal physiological changes in blood pressure [22]. The transplanted heart has a lower cardiac index (CI) and heart rate variability (HRV), high stroke volume, loss of cardiopulmonary baroreflexes, altered diastolic function of the ventricles, and temporary sinus node dysfunction. The denervated heart has depleted stores of norepinephrine within its nerve terminals. Reduced presynaptic neuronal uptake of catecholamines predisposes heart transplant patients to increased frequency of arrhythmias due to increased sensitivity to circulating endogenous catecholamines [23, 24]. Abnormal chronotropic response to exercise, abnormal catecholamine release and hemodynamic response to exercise and tyramine injection and impaired exercise capacitance is seen for as long as 1 year after heart transplant [25, 26].

Variable response to systemically administered adrenergic agonists and antagonists is seen in a transplanted heart as it is not controlled by sympathetic or parasympathetic nervous system. Since a transplanted heart has internally depleted catecholamine stores and depends on catecholamines circulating in blood, transplanted patients have increased propensity to develop arrhythmias. The use of β-blockers should be cautious in heart transplant patients as these medications adversely affect exercise tolerance of patients in the post-operative period. Loss of vagal innervation to the heart makes it unresponsive to the effects of atropine or digoxin, hence they are not recommended for treatment of brady or tachy arrhythmias in the postoperative period [27]. Bradyarrhythmias in the postoperative period are

treated with non-selective β-agonists, isoproterenol or via temporary or permanent pacing. Tachyarrhythmias in the postoperative period are responsive to rate control by amiodarone or diltiazem and could be indicative of transplant rejection.

7.2.4.4 Reinnervation of Transplanted Heart

Several studies done using Iodine-123 Metaiodobenzylguanidine (MIBG), tyramine have shown sympathetic reinnervation of the transplanted heart after a period of 6–12 months [28]. Wilson et al., in their study showed heterogeneous sympathetic reinnervation of sinoatrial node and left ventricle in patients 1 year or more after heart transplant [29]. Uberfuhr in his study showed minimal or no sympathetic reinnervation in first year post transplant but upto 80% from third year onwards followed by plateau in the process [30]. Sympathetic reinnervation of heart improves exercise tolerance of the patients in post-transplant period and patients can also feel anginal pain after sensory reinnervation of the transplanted heart as described by Stark et al. [31] In comparison to sympathetic innervation, parasympathetic reinnervation of transplanted heart takes about 12–36 months and is dependent on surgical technique used for transplant. In their study Bernardi et al. compared the effect of "standard" surgical technique with "bicaval" method of transplant [32]. In Standard technique, most of the recipient atria is left intact which helps preserve majority of innate parasympathetic axons. Bicaval technique removes almost all of the sympathetic and parasympathetic innervation as the entire atrial junctions of both superior and inferior venae cavae of the recipient are removed and substituted with corresponding chambers of the donor heart. Because of the variation in the innervation of the heart by the two surgical techniques, sympathetic and parasympathetic reinnervation can be stimulated in heart transplanted with bicaval method, whereas reinnervation in "standard" transplanted heart has been found to be unsuccessful.

7.2.5 Chronic Pain After Sternotomy

Chronic pain after sternotomy is an underdiagnosed entity in clinical practice. Post-sternotomy neuralgia was first described by Defalque and Bromley in 1989 [33]. Incidence of neuropathic pain after sternotomy has been reported to be between 11 and 56% [34]. Persistent post sternotomy pain can potentially contribute to decreasing the quality of life or can be severe enough to impair activities of daily life. Patients suffering from post-sternotomy pain report numbness, pins and needles, burning and stabbing sensation or aches at the surgical site [35]. Patients complain of persistent chronic pain at the graft harvest site due to injury to nerves during harvest or compression during suturing [36]. Irritation by sternal wires has also been identified as a potential etiology for the neuralgia. Removal of sternal wires after ruling out other etiologies and sternal instability has shown to be beneficial in the management of chronic post-sternotomy neuropathic pain [37].

Pain after cardiac surgery can improve with recovery of the patient. It responds well to opioid and non-opioid medication administration, intraoperatively and in the immediate postoperative period. Patients undergoing cardiac transplant are more likely to be chronically ill and harboring risk factors for the development of chronic pain such as pre-existing sternotomy and presence of preoperative pain [38].

Cardiothoracic anesthesiologists and surgeons are working collectively towards enhanced recovery after surgery (ERAS) to decrease morbidity and mortality in patients. Over the past few years, the focus has been given to preoperative patient counselling, decreased use of opioids, multimodal analgesia, regional anesthesia, early ambulation and improved outcomes in postoperative period.

7.3 Management

7.3.1 Patient Counselling

It is thought that patients who are actively involved in the management of their health show improved outcomes after surgery [39]. Policies and strategies should be developed to strengthen involvement of the patients in their healthcare to enhance positive outcomes [39]. Several studies have identified preoperative anxiety as a potential contributor to the development of chronic postoperative pain [2, 3]. Greszta et al. has discussed the relationship between the level of anxiety with increased consumption of analgesics by patients after cardiac surgery [40]. Preoperative patient counselling can significantly improve the perception of postoperative pain by patients after cardiac surgery. Several studies have identified pre-existing pain, low preoperative pain threshold, presence of preoperative chronic pain, low preoperative pain tolerance, personality traits, and patient mood and affect to have a positive correlation with postoperative pain and consumption of analgesics in postoperative period [41–44]. Ronaldson et al. has shown a positive correlation between optimism and positive expectations with improved recovery and favourable long term outcomes after cardiac surgery [45]. Psychology consultation and counselling should be offered to help patients cope and get more actively involved in their recovery after a heart transplant. Patient should be evaluated thoroughly preoperatively for factors that could modify and guide adequate postoperative pain management. Several tools listed in Table 7.2 are available for anxiety, pain threshold levels and psychological assessment of patients in the preoperative period.

7.3.2 Pharmacological Management

Pharmacological therapies utilizing both opioid and non-opioid based postoperative analgesic management have been found to be effective. Over the past several decades intravenous opioids have been routinely administered to provide

Table 7.2 Psychological and pain measurmenet scales [46]

Psychological measurement scales	Pain threshold measurement scales
1. Hospital Anxiety and Depression Scale 2. Self-rating Questionnaire for Depression 3. State-Trait Anxiety Inventory 4. Mental Health inventory 5. 26-Item Stress Scale 6. Illness Behavior Questionnaire Disease Conviction Scale 7. Minnesota Multiphasic Personality Inventory (MMPI) 8. Eysenck Personality Questionnaire (EPQ) 9. Brief COPE (Coping scale) 10. Pain Catastrophizing Scale	1. Sensory, Mechanical Pain Threshold and Heat Pain Threshold and Perception 2. Electronic Pressure Algometer 3. Suprathreshold Pain

immediate relief for acute postoperative pain. Side effects with increased use of opioids such as sedation, respiratory depression, nausea, vomiting, ileus, and urinary retention are well established. These side effects contribute to increased duration of stay in intensive care units. With an emphasis on enhanced recovery after surgery for cardiac surgeries, multimodal approach to postoperative analgesia is most frequently recommended. This approach helps decrease the side effects of individual medications and utilizes the synergistic effect of medications via different pathways to enhance early extubation and ambulation. Physicians have been increasingly using opioid sparing medications such as acetaminophen, dexmedetomedine, local anesthetics, clonidine, ketamine, gabapentin, non-steroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase (COX) inhibitors as part of pharmacological multimodal analgesia regimens. Intravenous patient controlled analgesia that continuously or intermittently infuses opioid or nonopioid medications can also be used to provide adequate analgesia in the postoperative period. Although several medications are available to adequately manage postoperative pain, studies have reported patient dissatisfaction with the provided management [47]. This brings emphasis to continued patient, family and nursing staff education in the postoperative period to optimize and appropriately administer medications for adequate pain management.

7.3.3 Interventions

ERAS focuses on improving postoperative morbidity and mortality and reducing the financial burden on the patients and hospitals. Poor postoperative pain control could be contributory to delayed recovery and discharge from the intensive care unit. Preemptive analgesia to improve postoperative pain control should be consid-

ered where feasible. Use of preemptive analgesia with neuroaxial blockade has shown to reduce the incidence of perioperative arrhythmia, inflammatory response, pulmonary complications and pain scores after cardiac surgery [48, 49]. Neuroaxial blocks with indwelling catheters for continuous infusion in the postoperative period could be most beneficial but has limitations as it could be associated with catastrophic epidural hematoma formation due to complete heparinization during cardiopulmonary bypass. Studies have shown regional blocks under guidance of ultrasound to be relatively safe even in patients who are anticoagulated preoperatively [50, 51]. Perforating branches of intercostal nerves, arising from anterior rami of thoracic spinal nerves from T1 to T11 provide sensory innervation to chest wall. Most of the sensory supply of the thoracic chest wall is provided by the anterior divisions of T2–T6 intercostal nerves, T7 terminates at the Xiphoid process. Nerve branches of T8–T11 provide sensory supply to the anterior abdominal wall. Various regional blocks such as paravertebral block, serratus anterior plane block, pectoral nerve block (PECS—I & II) are performed under ultrasound guidance after induction of general anesthesia. They can be used to block these perforating branches at different levels to provide adequate analgesia for thoracotomy or minimally invasive cardiac surgery. Heart transplant requires midline sternotomy incision and has its own challenges for regional blockade. The most described and appreciated block for midline sternotomy is bilateral Parasternal intercostal block. This block can be performed by the surgeons by infiltration of local anesthetic in the field before closure of sternotomy or by continuous infusion of medications through bilateral parasternal catheters in the postoperative period [52]. The use of sternal wound subcutaneous catheter for continuous infusion of local anesthetics in the postoperative period has also been described in the literature with positive outcomes, but has shown to have associated increased risk of wound infection [53, 54]. Ultrasound guided bilateral erector spinae plane block,bilateral paravertebral blocks or bilateral paravertebral catheters have been successfully utilized to achieve optimum pain control in the postoperative period [55, 56]. Variable concentration of ropivacaine, bupivacaine and levobupivacaine have been used to achieve the desired effects. These blocks can be safely performed using ultrasound guidance after completion of the surgery and reversal of anticoagulation to extend the effect of analgesia in the postoperative period. With use of local anesthetics as bolus or continuous infusion along with local infiltration at the harvest site or chest tube site, one should always be watchful for local anesthetic toxicity. After assessing risk benefit ratio, comfort and skill levels of the physician regional nerve blocks could be extensively used to provide multimodal analgesia to patients undergoing cardiac surgery.

7.3.4 Other Modalities

Ozturk et al. compared paravertebral block with transcutaneous electrical nerve stimulation (TENS) for pain management after cardiac surgery [57]. Study failed to prove superiority of TENS over regional block in regards of opioid consumption but

did show decreased opioid consumption when compared to placebo. TENS is relatively safe, noninvasive, effective and has shown to reduce opioid consumption. It could be offered to patients as part of the management of postoperative pain.

Patients have also been shown to respond well to nontraditional methods like perioperative massage, music therapy, acupuncture [58, 59]. Positive response to these nontraditional methods could be because they help in relaxation, relieving anxiety and muscle tension that could improve mental well-being of the patients resulting in improved responsiveness to ongoing pain management.

7.4 Pain Assessment Tools

Several validated pain assessment tools have been developed for optimization of pain management in postoperative period. These tools or scales are developed to assess pain in varied patient groups depending upon age, cognitive development, level of consciousness/sedation, level of education, and cultural or language differences. Behavioral Pain Scale and the Critical-Care Pain Observation Tool are available for assessment of pain in intensive care settings. Along with physiological indicators, physicians should use these tools to assess the response to ongoing pain management and modify the treatment to improve patient experience. Gelinas et al. studied 105 intubated and sedated cardiac surgery patients in intensive care unit. Although the study had limitations, it validated the reliability of Critical-Care Pain Observation Tool for assessment of pain in sedated patients to modify ongoing management [60]. Aïssaoui et al. validated the reliability of Behavioral Pain Scale in ventilated critically ill patients [61]. Various scales to assess the severity of pain in intubated non-communicative or patients who can self-report their pain are listed in Table 7.3:

Table 7.3 Pain assessment tools

Verbal descriptor scale	Non-verbal descriptive scale
1. Face Rating Scale: (a) Oucher Scale (b) Wong-Baker faces scale (c) Revised Faces Pain Scale 2. Pain Thermometer Scales 3. Numeric Rating Scale (NRS) (a) Six-point NRS (b) Eleven-point NRS (c) Twenty-one point NRS 4. Visual Analogue Scales 5. Verbal Rating Scales (VRS) (a) Four-point VRS (b) Seven-point Graphic Rating Scale (c) Six-point Present Pain Inventory (PPI)	1. CPOT: Critical-Care Pain Observation Tool 2. BPS: Behavioral Pain Scale 3. ANVPS: Adult Nonverbal Pain Scale 4. COMFORT 5. FACES-nurse 6. FLACC: Face, Legs, Activity, Cry, Consolability scale 7. PABS: Pain Assessment Behavior Scale

Nonverbal descriptive scales are used to optimize pain management while patients are intubated and sedated in ICU. These validated scales involve assessment of facial expression, movement of extremities, changes in vital signs, muscle tension, respiratory distress and other parameters individualized to each scale for assessment. Once patients are extubated and can self-report verbal descriptive scales should be brought in clinical use for optimization of postoperative pain management.

7.5 Challenges in the Management of Pain While in the Hospital

- *Managing expectations of pain after surgery:* Patients should receive thorough counselling regarding postoperative pain management during their preoperative anesthesia evaluation by anesthesiologist or acute pain medicine physician. Patients should be provided with counselling regarding the severity of the pain, its duration, and modalities of treatment planned. Patients should also be made aware of the different pain assessment tools that will be used while they are intubated. Expectations should never be set to achieve complete pain control. Patients should be made aware of breakthrough pains.
- *Psychological status of the patient:* Various studies listed in this chapter have repeatedly emphasized that preoperative anxiety, depression and other mood changes have significant impact on the outcome of management of pain after surgery. Once the preoperative psychological evaluation is done in preparation for the heart transplant, patients with diagnosed mood disorders should have a management plan in place to help improve their mental health. They could receive pharmacological or behavioural therapy with scheduled follow ups to help improve their mood disorders. A study done on 197 patients undergoing cardiac surgery has shown that preoperative optimism has a positive impact in the postoperative period [45]. This study by Ronaldson emphasised that greater optimism measured pre-operatively was significantly associated with lower pain intensity and fewer physical symptoms following surgery.
- *Nursing:* Nurses taking care of patients in intensive care units are the first point of contact for patients while recovering in ICU after heart transplant. Information collected by them is helpful in decision making by physicians. Nurses receiving training for management of patients after heart transplant should also receive extensive training to assess and document pain scores in ventilated and sedated patients. Daily review of data collected accurately by nurse can give a very accurate assessment of pain control by ongoing treatment and help modify the treatment in sedated patients. Timely administration of scheduled medication and continuous maintenance of ongoing infusions without long breaks could be helpful in maintaining adequate control, prevention and management of breakthrough episodes of pain. Good communication between physicians and nursing is key to provide the best possible care to the patients.

- *Assessment of pain*: Assessment of pain in the postoperative period could be challenging in cardiac surgery patients. Transplanted heart is denervated and patients cannot perceive pain of cardiac origin but referred pain should always be investigated after surgery to rule out nerve injury or entrapment. Cardiac ischemia secondary to inadequate revascularization or new coronary artery disease, aortic dissection, Dressler's syndrome, hemo or pneumothorax after removal of drains, and sternal wound infection should always be ruled out while evaluating patients for reports of worsening of ongoing pain or new onset pain after cardiac surgery.
- *Immunosuppression:* Use of high dose opioids is associated with immunosuppression in the post-operative period. In his study Welters et al. showed suppression of granulocyte chemotaxis and neutrophil function on exposure to morphine [62]. He also demonstrated dose and time dependent reduction of complement and immunoglobulin receptor expression on the surface of neutrophils after exposure to morphine. Use of high dose morphine in the postoperative period has been identified as a modifiable risk factor associated with nosocomial pneumonia in elderly patients after cardiac surgery [63]. Although use is opioids is an integral part of multimodal analgesia, failure to timely assess pain scores and continued administration of high dose opioids has been reported to be associated with increased incidence of surgical site infection and nosocomial pneumonia in the postoperative period [64].

7.6 Management of Pain in the Inpatient Setting

Pain management in patients after heart transplant has several challenges. Although many modalities of pain management are available, few can be applied in cardiac transplant patients due to the nature of the surgery and the coagulation changes that takes place with heparinization and cardiopulmonary bypass. Some of the safer modalities and medications are:

1. *Opioids:* Routinely prescribed medications for postoperative pain management. They are titrated according to the severity of pain assessed or reported. Non-judicious use of opioids could delay extubation of the patient or could result in delayed respiratory depression after extubation. Opioids should be combined with other analgesics to decrease side effects and to support ERAS.
2. *Non opioid medications:* Non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen and metamizole have been safely used as part of multimodal analgesia in cardiac surgery patients.
3. *Patient controlled analgesia (PCA):* Use of microprocessor controlled infusion pumps in the postoperative period for administration of opioids are very helpful in providing a continuous administration of opioids, reducing episodes of breakthrough pain and preventing opioid overdose. These pumps can be used to provide a set calculated dose of continuous infusion of medication and bolus dose

intermittently at pre-selected intervals. These pumps do not require training for use and can be easily used by nurses when patients are sedated and by patients when they are awake enough to actively participate in their care.

4. *Local anesthetic:* Skin infiltration with local anesthetic before making incision for preemptive analgesia is also helpful in decreasing peripheral and central sensitization and systemic response to sternotomy. Infiltration of surgical wound and drain sites with local anesthetics at closure could have an additive effect on postoperative pain management.
5. *Regional block:* One can safely use ultrasound guided single shot regional blocks preoperatively or after reversal of heparinization and surgical closure to extend the duration of pain relief in postoperative period.
6. *Regional catheters:* Studies as mentioned earlier in the chapter, have shown the effectiveness and safety of regional catheter use for infusion of local anesthetics for postoperative pain relief. This practice varies across institutions depending upon the comfort of surgeons and anesthesia providers or request by the patient.
7. *Anticonvulsants:* Meta-analysis performed by Maitra et al. have shown that perioperative use of pregabalin and gabapentin (2 h prior to surgery and continued in the postoperative period) lowers pain scores in the postoperative period, although there is no significant difference between postoperative consumption of opioids as compared to placebo [65].

Note: Thoracic epidurals and paravertebral blocks are considered as "gold standard" for postoperative pain management in thoracic surgeries [66, 67]. They are a part of ERAS protocol for thoracic surgery allowing early mobilization and reduced opioid consumption. These blocks have limited utilization in cardiac surgery because of the risk of hematoma formation with heparinization which can be devastating to the patients

7.7 Management of Heart Transplant Patient Presenting to Emergency Department

With improving survival and longevity of transplant patients, physicians can come across heart transplant recipients in the emergency department (ED) with varied presentation. Orthotopic heart transplant patients will not present to the ED with chest pain for several months after the transplant secondary to denervation related with surgery. Failure of transplant patients to report typical systemic symptoms even after several years of transplant owing to alterations in normal anatomy and physiology by multiple contributory factors should not trivialize their presentation to the hospital with minor symptoms and should initiate early multidisciplinary involvement and thorough workup to rule out transplant rejection and avoid detrimental outcome of the patient. Thorough workup should be done to rule out graft rejection, surgical site or systemic infection, ongoing ischemic cardiac event, arrhythmias and vascular dissection. While managing patients presenting to the ED

after trauma the alteration in the physiology mentioned earlier in the chapter should be kept in mind. Transplanted heart does not respond to atropine, hence along with volume replacement epinephrine, norepinephrine and isoproterenol should be used for optimization of hemodynamics in trauma patients.

Acute pain management team should be involved early in the care of transplant patients presenting with trauma to achieve adequate pain control that will have a positive effect on the surging catecholamine levels and hemodynamics of the transplant patients. Various modalities mentioned in the chapter can be utilized to achieve adequate pain control in trauma patients. These modalities should be individualized for every patient after thorough assessment of mental status, hemodynamics, medication reviews and patient preference when able.

7.8 Discharge Plan for Pain Management

1. Family support.
2. Appointment for follow ups as outpatient.
3. Access to psychological support as outpatient.
4. Medical prescription with counselling for adequate use of medications.
5. Counselling regarding coming back to hospital or reaching out to the physician when required.
6. Information regarding non-conventional approaches to pain management.
7. Counselling regarding phase of recovery and changes patients should expect in the postoperative period.

Cardiac transplant is a challenging surgery for both care providers and patients. It requires a tremendous amount of preparation by medical personnel and patients alike. A team of several physicians work together and prepare the patient for transplant and a successful outcome. Patients describe this procedure as a life changing experience because when the transplant is successful, they experience significant improvement in their quality of life. Patients require constant support in the postoperative period to maintain a good level of quality of life after the surgery.

Cardiac transplantation is a complex surgery and can result in a prolonged recovery period. Failure of improvement of pain or persistence of pain while in the hospital and after discharge could be devastating to patients. Poor pain control is an important contributory factor for delayed recovery of the patient, increased duration of ICU care, increased risk of morbidity, financial burden on patients and hospitals and loss of productive days of when patients return back to their lives. Development of chronic pain after surgery can negatively affect the mental health of the patients. Chronic pain has been identified as a risk for suicidal ideations and attempts by the patients to end their suffering [68]. Use of multimodal analgesia, continuous evaluation of patients for optimization of treatment, perioperative psychological evaluation and management to repeatedly educate the patients to be optimistic and actively

participate in their care, and effective communication between care providing teams and patients could be some of the key factors to enable the patients to actively participate in their care and improve their experience during the recovery period.

7.9 Summary

A brief summary of in-patient pain management and discharge planning for pain management is listed below:

Multimodal approach:

- Patient Counselling.
- Opioids- Intravenous, PCA, patches or PO when able.
- Non opioids—NSAIDs, Acetaminophen, Metamizole.
- Ultrasound guided regional blocks—before or after surgery.
- Infiltration of surgical incision and drain sites with local anesthetics.
- Continuous Peripheral Regional blocks—after reversal of heparinization.
- Psychological evaluation and management.
- Transcutaneous electrical nerve stimulation.
- Non-conventional therapies—Music, massage, acupuncture.

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Chapter 8
Patient with a Cardiac Implantable Device

Ramsey Saad, Derrick Williams, and Nabil Sibai

8.1 Introduction

The inpatient setting poses different challenges to the pain provider compared to presentation of patients in the outpatient setting. Patients may present with a higher degree of acuity, which is usually associated with a prompter expectation of pain relief. If interventions are to be offered, the expectation for them is to be performed on an urgent basis. On the other hand, special care should be taken into consideration regarding the patient's medical condition. Communication between different care teams is paramount, to ensure safety and effectiveness of treatment. If the implantable cardiac device was placed at an external facility, communication with the physician/service who underwent the initial implant, in addition to the device manufacturer is key to ensure safe and effective treatment.

8.2 Pathophysiology and Risk Factors

Commonly used implantable devices include; pacemakers, automated implantable cardiac defibrillators (AICD) and left ventricular assist devices (LVAD).

The most common indication for cardiac Pacemakers is bradyarrhythmias. Some patients with a permanent pacemaker require an upgrade to an implantable cardioverter-defibrillator (ICD). All functions are usually served by one pulse generator [1].

The most common indications for permanent pacemaker implantation are sinus node dysfunction and high-grade or symptomatic atrioventricular (AV) block.

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Guidelines for implantation of cardiac pacemakers have been published jointly by the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society (ACC/AHA/HRS) [2].

8.3 Types of Permanent Pacemaker Systems

All cardiac pacemakers consist of two components: a pulse generator, which provides the electrical impulse; and one or more electrodes (commonly referred to as leads), which deliver the electrical impulse from the pulse generator to the myocardium.

Transvenous systems: Which is used by most cardiac pacing systems.

Epicardial systems: which utilize a pulse generator with leads that are surgically attached directly to the epicardial surface of the heart. The major role for epicardial pacing systems in current practice is for temporary pacing following cardiac surgery.

Leadless systems: In response to the limitations of both transvenous and epicardial pacing systems, efforts have been made to develop leadless cardiac pacing systems [3–10]. Initial leadless systems involved multiple components but were associated with high complication rates [3].

Leadless cardiac pacing systems have been approved for use in Europe since 2013, and in April 2016, the first leadless cardiac pacing system was approved for use in the United States [11].

In 2016, the Nanostim manufacturer issued an alert regarding battery malfunction occurring between 29- and 37-months post-implant and therefore implantation of any further Nanostim devices was suspended [11].

Leadless cardiac pacing appears both safe and efficacious in the short term, however, longer-term follow-up is needed to determine these devices' safety [1].

8.4 Ventricular Assist Devices (VADs)

A VAD can be used as a bridge to cardiac transplantation (until a donor heart becomes available), as a bridge to decision (regarding candidacy for cardiac transplantation), as destination (or permanent) therapy, or as a temporary measure until recovery of heart function. Most patients receiving mechanical cardiac support for these indications receive a left ventricular assist device (LVAD), other options are receiving biventricular support in the form of biventricular device (BiVAD; left plus right ventricular support) or total artificial heart (TAH) [12, 13].

8.5 Management of Pain During Inpatient Hospital Stay

8.5.1 Non Pharmacologic Modalities

Physical therapy: If the patient is a candidate for physical therapy, any limitations with therapy should be discussed with the cardiologist.

Transcutaneous Electrical Nerve Stimulation (TENS): The use of TENS is not recommended in patients with AICD as noise reversion and undersensing might prevent ICD from delivering shock when needed [14].

Radiofrequency Ablation (RFA): Special precautions should be taken should RFA be considered on patients with implantable cardiac devices:

- Ensure that temporary pacing and defibrillation equipment is available.
- Avoid direct contact between the ablation catheter and the implanted system.
- Position the return electrode patch so that the electrical current pathway does not pass through or near the device and leads.
- Always monitor the patient during ablation with at least two separate methods, such as arterial pressure display, ECG, manual monitoring of the patient's rhythm (taking pulse) or monitor by some other means such as ear or finger pulse oximetry, or Doppler pulse detection.
- In the case of pacemakers, to avoid or mitigate the effects of oversensing, if appropriate for the patient, initiate asynchronous pacing by implementing one of the following precautions;
- Suspend tachyarrhythmia detection by using a magnet or a programmer. If a programmer is used and ablation causes a device reset, the cardiac device resumes detection. After the ablation procedure, remove the magnet or restore device parameters.
- If appropriate for the patient, program the device to an asynchronous pacing mode (for example, DOO). After the ablation procedure, remove the magnet or restore device parameters [15].

8.5.2 Spinal Cord Stimulation

When a patient's medical condition requires both a neurostimulator and an implanted cardiac device (e.g., pacemaker, defibrillator), physicians involved with both devices (e.g., neurologist, neurosurgeon, cardiologist, cardiac surgeon) should discuss the possible interactions between the devices before surgery.

The electrical pulses from the neurostimulation system may interact with the sensing operation from a cardiac device and could result in an inappropriate response of the cardiac device. To minimize or prevent the cardiac device from sensing the neurostimulator output:

– Implant the devices on opposite sides of the body
– Program the neurostimulator therapy output to a bipolar configuration
– Consider using bipolar sensing on the cardiac device

Careful programming and review of each system's performance is necessary to ensure safe cardiac system operation with effective neurostimulation therapy [16].

8.5.3 Intrathecal Drug Delivery Systems (IDDS)

When a patient has a programmable pump and another active implanted device (e.g., pacemaker, defibrillator, neurostimulator):

– The radiofrequency (RF) signal used to program either device can reset or reprogram the other device.
– The magnet in a cardiac programmer may temporarily stop the pump.

To verify that inadvertent programming did not occur, clinicians familiar with each device should check the programmed parameters of each device before the patient is discharged from the hospital and after each programming session of either device (or as soon as possible after these times).

Also, inform patients to contact their physician immediately if they experience symptoms that could be related to either device or to the medical condition treated by either device [17].

8.6 Therapeutic Radiation

External beam ionizing radiation places the CIED at risk of malfunction or reversion to safety mode. In most cases, the CIED is avoided from the radiation beam, however it is recommended that patients undergoing therapeutic radiation enroll in a remote device monitoring program. In high risk cases (such as chest radiation) the recommendation is for the device to be evaluated within 24 h of completing radiation [18].

8.7 Electroconvulsive Therapy (ECT)

There have been case reports describing interference of ECT with CIEDs. The noise reversion mode may be triggered, in addition to myopotential oversensing from seizure activity. Sinus tachycardia may also cause inappropriate shock by ICD. The main concern would be if a prolonged stimulus is used. If so, the pacemaker should be programmed in asynchronous mode, and unipolar mode should be avoided in pacemaker—dependent patients. A magnet should also be readily available. Beta blockade prior to treatment, to avoid tachycardia, should also be considered. Device interrogation within a month after undergoing ECT is recommended [18].

8.8 Practical Considerations in Patients with Ventricular Assist Devices

Patients supported by ventricular assist devices (VADs) need to be treated with anticoagulant and antiplatelet agents to reduce the risk of thrombotic complications such as device thrombosis and embolic stroke, therefore the risk and benefit of

holding anticoagulation and antiplatelet therapy should be taken into account should any interventions be considered [19–21].

Given the reduced arterial pulse pressure seen in these patients, blood pressure is best estimated using a Doppler ultrasound probe and sphygmomanometer (generally brachial) [22]. Consultation with Cardiology service and device manufacturer may be beneficial for ideal monitoring during procedures.

8.9 Pharmacologic Modalities

The use of systemic lidocaine (for infusion therapy) and its oral congeners (mexiletine) have been used as a treatment modality for neuropathic pain management [23]. Mexiletine and systemic lidocaine are contraindicated in second- or third-degree heart block, except in patients with an artificial functioning pacemaker [24, 25].

Undergoing **ketamine** infusions for chronic pain is accepted practice in many institutions [26]. This medication, though, has significant cardiovascular side effects such as increasing blood pressure, heart rate, and cardiac output. These side effects should be taken into consideration when considering performing ketamine infusions in patients with coronary artery disease and also in patients with known arrhythmias [27].

The use of nonsteroidal anti-inflammatory drug (NSAID) therapy is associated with increased risk of cardiovascular events, the risk being increased in the presence of prior cardiovascular disease, history of systemic inflammatory disorder, older age, and male gender, as well as hypertension, hyperlipidemia, diabetes, and smoking [28]. Some but not all case-control studies have suggested a modest increased risk for the development of atrial fibrillation in patients taking NSAIDs [29, 30].

Methadone is an opioid which can be used for chronic pain in addition to its well documented role for maintenance programs for patients recovering from opioid abuse. One of the concerns though, is Qtc prolongation, the development of Torsades de Pointes (TDP) and possibly sudden death. AICD implantation may be protective in allowing patients to complete methadone programs [31].

Hydrocodone QTc prolongation has been observed with hydrocodone ER, especially following doses of 160 mg/day. It is recommended to be used with caution in patients with congestive heart failure, known arrhythmias, electrolyte abnormalities or in patient using other medications known to prolong the QTc interval. It is also recommended to be avoided in patients with congenital long QT syndrome [32].

Fentanyl is an opioid which may be used for opioid tolerant patients (in the transdermal form) in addition to its use for breakthrough pain (either in the intravenous form or for breakthrough cancer pain in the form of lozenge, buccal, intranasal or sublingual form). It may have cardiovascular side effects in 1–10% of the population, in the form of atrial fibrillation, bigeminy, cardiac arrhythmia, hypertension, hypotension, sinus tachycardia, syncope, tachycardia and vasodilation. These potential side effects should be taken into consideration prior to prescribing in patients with known arrhythmias [33].

Other opioids such as oxycodone, though not known to directly affect the Qtc interval, they may cause severe hypotension (including orthostatic hypotension and

syncope); and it is recommended to be used with caution in patients with hypovolemia, cardiovascular disease, or drugs which may exaggerate hypotension [34].

The use of ondansetron for nausea (occasionally also related to opioid use) may be associated with QT prolongation. Cases of torsades de pointes have also been reported. This is more so in the intravenous form compared to the oral form, and in doses greater than 32 mg. Single doses >16 mg ondansetron IV are no longer recommended due to the potential for an increased risk of QT prolongation. In most patients, these changes are not clinically palpable; however, when used in conjunction with other agents that prolong these intervals or in those at risk for QT prolongation, arrhythmia may occur. Ondansetron use should be avoided in patients with congenital long QT syndrome. The risks and benefits of administration, in addition to the appropriate monitoring should be taken into consideration in patients with other risk factors for QT prolongation [35, 36].

Certain antidepressants, which may also be effective for neuropathic pain such as **amitriptyline** should be used with caution in patients with conduction abnormalities, due to the high risk of developing heart block [37]. Nortriptyline should be avoided in patients with Brugada syndrome [38].

8.10 Other Challenges in Management of Pain While in the Hospital

8.10.1 Diagnostic Imaging

8.10.1.1 Magnetic Resonance Imaging (MRI)

Coordination between radiology and cardiology is strongly advised prior to considering undergoing MRI on patients with cardiovascular implantable electronic devices (CIED). Moreover, patients with a pacemaker or intracardiac defibrillator in place who undergo MRI should be under the care of a cardiologist before, during, and after their exam [39].

The majority of the CIEDs in the United States population are classified as MRI unsafe [40, 41]. In most scenarios, this is a contraindication to MRI [39, 42, 43].

Many modern CIEDs have been designed to be MRI conditional, which be identified by model name, number, and manufacturer at MRIsafety.com

Even if the CIED is labeled MRI conditional a cardiac evaluation remains to be of utmost importance to rule out contraindications to undergoing MRI, for example disconnected pacer leads are at risk of heating [39, 44].

8.10.1.2 Computerized Tomography (CT) and X-Ray

CT is a well-accepted imaging choice with patients with CIEDs, with the risk of adverse events considered extremely low. However, per FDA recommendations, the current understanding is that when a CT scanner directly irradiates the circuitry of

certain implantable electronic medical devices (i.e. when the device is visible in the resulting CT image), it can cause sufficient electronic interference to affect the function and operation of the medical device.

The probability that this can cause significant adverse events remains to be extremely low. The probability of **x-ray** electronic interference is lower when the radiation dose and the radiation dose rate are reduced.

Per FDA recommendations, interference is completely avoided when the medical device is outside of the primary x-ray beam of the CT scanner [45].

8.10.1.3 Ultrasound

Ultrasound is a well-accepted modality of imaging for patients with CIEDs.

8.11 Electromyography (EMG) and Nerve Conduction Studies

Given the small amount of current used in these studies, there have been no published cases of device malfunction, even if performed in close proximity to the devices [18].

8.12 Considerations for CIEDs in the OR Setting

Due to the dramatic rise in the use of these devices over the past two decades, the modern anesthesiologist has seen a steady rise in patients with CIED's in the operating room. These patients have numerous considerations that the clinician must take into account when creating an anesthetic plan. The 2011 HRS/American Society of Anesthesiologists Expert Consensus Statement created by the American Heart Association, the American College of Cardiology, and the Society of Thoracic Surgeons was devised to provide guidelines for perioperative management of patients with CIED's [18].

The perioperative setting provides unique challenges in the care of patients with these specific implantable devices such as, the presence of electrical interference, alterations in electrolytes, pH, and temperature (due to large blood loss or fluid shifts), and the possibility of device malfunction intraoperatively. Patients with CIEDs almost universally have systolic heart failure, concomitant ventricular dyssynchrony, or are subject to malignant arrhythmias such as ventricular tachycardia or fibrillation. Perioperative management must start with a rigorous preoperative assessment that should acquire this information:

- Specific surgical procedure and location.
- Type of electrocautery to be used.
- All other sources of electromagnetic interference (EMI).
- Patient positioning.

- Anticipated large blood loss or fluid shifts.
- Type and function of the CIED.
- Manufacturer and model.
- Indication for implantation.
- CIED program details.
- Pacer dependency.
- Interrogation information (within past 12 months for permanent pacemakers and past 6 months for ICD's) [46].

Acquisition of this information will allow for the crafting of an appropriate anesthetic plan that will avoid device damage, hemodynamic abnormalities, inappropriate CIED therapy, inadvertent electrical reset to backup pacing modes, or malignant arrhythmias due to device malfunction [18, 47].

There is a widespread thought that intraoperative management of CIED's involves simply placing a magnet on it to disable the anti-tachycardia functions. However, it is important to note that magnets may result in a wide range of responses depending on the manufacturer and type of device. Additionally, the device can be programmed in a manner that is atypical for that given device type [46]. *It is important that the anesthesiologist determine the type and function of the CIED as part of the preoperative assessment (look at later)* It is critical that the clinician understand the difference in responses to a magnet. Pacemakers typically respond to magnet placement by reverting to an asynchronous mode of pacing. Removal leads to a restoration of the former device pacing program [47]. Implantable cardioverter defibrillators (ICDs) typically respond to magnet placement by disabling the anti-tachycardia function, as mentioned previously. However, it can be programmed to ignore the magnet application, so it is critical to contact the implanting EP physician or manufacturer programmer to determine if this has been done. A magnet will not affect the pacing function of an ICD.

Intraoperatively, the anesthesiologist must assure that the patient with a CIED is monitored for intraoperative arrhythmias potentially due to interference from EMI. If it has been determined that a magnet will deactivate the anti-tachycardia function, all patients must have defibrillator pads placed and be monitored closely for hemodynamic changes that may arise from EMI induced dysrhythmias [48].

8.13 Special Considerations for CIEDs in the Emergency Setting

Evaluation of medical record, patient registration card, review of available chest radiographs, communication with the device company are useful tools for identification of the device type. Obtaining a 12-lead electrocardiogram may be useful to assess pacemaker-dependency. Monitoring the patient with arterial line, having transcutaneous pacing and external defibrillator pads, and in case of ICD, evaluation of function prior to leaving monitored setting is essential. Contact with CIED team and device manufacturer as soon as feasibly possible is very important as well. In

case of pacemaker dependency and in presence of ICD, placing a magnet over the device to suspend tachyarrhythmia detection and using short electrosurgical bursts is important. In the case of pacemaker dependency and in absence of ICD, place magnet only for surgeries above the umbilicus and having a magnet available for procedures below the level of the umbilicus is recommended [18].

8.14 Discharge Plan for Pain Management

Prior to discharge, the patient should be stable from the cardiac standpoint. Adequate interrogation of the device, and the necessary outpatient follow up should be coordinated with the cardiology/electrophysiology team. Should any prescribed medications for pain such as opioids, NSAIDs or mexiletine be considered long term, the risks and benefits of long-term use should be discussed with the patient. Outpatient follow up in a pain clinic is reasonable to determine the appropriateness of continuing medications and to monitor effectiveness of the treatment plan and any necessary adjustments or interventions that can be offered.

8.15 Summary

- Special Care should be taken into consideration when managing patients with CIEDs
- Careful evaluation of comorbidities, concomitant medications including anticoagulation and antiplatelet therapy is important in order to evaluate the most appropriate course of management
- Accurate review of medication list, in addition to adequate knowledge of side effect profile of medications is paramount to patient safety prior to prescribing medications or considering infusions on patients with known susceptibility to arrhythmias
- Coordination between radiology, cardiology and device manufacturer is paramount prior to undergoing imaging, particularly MRI, in addition to certain procedures (RFA) and implants
- Review of The Heart Rhythm Society (HRS)/American Society of Anesthesiologists (ASA) Expert Consensus Statement on the Perioperative Management of Patients with Implantable Defibrillators, Pacemakers and Arrhythmia Monitors is important for a safe outcome in the Operating Room setting

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Chapter 9
Patient with Liver Failure

Raj Desai and Nalini Sehgal

9.1 Introduction

In a systematic review of five studies, the prevalence of pain in patients with end-stage liver disease ranged from 30 to 79% [1]. Appropriate treatment of pain in hospitalized patients with liver failure is imperative for reducing complications and for safe discharge. Under treating pain in this population could potentially lead to inappropriate opioid use and dependence, deconditioning due to prolonged immobilization, increased risk for medical complications, longer hospital stays and poor patient and family satisfaction.

Treatment of pain in patients with liver failure can be medically complex due to pharmacologic, metabolic, excretion, and biopsychosocial factors. There can be potential fatal complications from analgesia in these patients leading to systemic toxicity, hepatic encephalopathy, GI bleeding and hepatorenal syndrome.

Multimodal treatments with behavioral therapies, rehabilitation therapies and interventional techniques must be employed to optimize pain control, and reduce analgesic use. Appropriately adjusting loading dose and maintenance dose, and slower rate of titration can result in successful pain treatment with lower risk of adverse effects.

9.2 Pathophysiology

The liver is the site for first pass metabolism, protein synthesis, enzyme activity (CYP-450), drug conjugation and biliary excretion.

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Hepatic failure reduces capacity of the liver to metabolize drugs. Changes in protein synthesis, enzyme activity (CYP450), drug conjugation, biliary excretion and hepatic blood flow alter drug metabolism and result in decreased hepatic clearance, and prolonged drug half-life**.**

Many of the oral analgesics and medications used in pain management undergo first pass metabolism in the liver. First-pass metabolism is reduced in patients with liver disease, resulting in increased proportion of the drug entering the systemic circulation and increasing the risk of systemic toxicity.

Many drugs are bound to plasma proteins, mainly to albumin and α1-acid glycoprotein. The synthesis of these proteins is impaired in liver with consequent reduction in protein binding of the drug, and increased availability of unbound free drug that can lead to systemic toxicity.

Liver failure is associated with reduced metabolic capacity for drugs that undergo oxidation and glucuronidation (via CYP-450). To complicate matters further, cytochrome enzymes exhibit genetic polymorphism.

9.3 Treatment

9.3.1 Non-pharmacological Management

Conservative non pharmacologic therapy must be employed as first line pain management in patients with liver failure. Physical modalities such as topical heat, cold, ultrasound, TENs unit can provide relief of pain. These modalities can also be used as adjunct to pharmacologic and interventional pain management.

Therapeutic heat over areas of localized pain is an effective method of pain control. Heat improves soft tissue elasticity, increases blood flow, metabolic activity, oxygen demand and capillary permeability. Examples of therapeutic heat include hydrocollator packs, fluid baths, heat wraps, and ultrasound diathermy. These modalities are contraindicated in presence of decreased sensation, acute inflammation, hemorrhage, malignancy, edema, peripheral vascular disease, and ischemia. The mechanism of heat transfer depends on the modality/device used and includes radiation (radiant lamps), conduction (heat packs. water baths), convection, conversion (ultrasound). Ultrasound is used for heat transfer to deeper structures (2–3 cm deep).

Therapeutic cold: tissue cooling causes local analgesia and muscle relaxation. Therapeutic cold causes local vasoconstriction, decreases metabolic activity and enzymatic activity, and decreases oxygen demand. Ice packs, ice massage, contrast baths and vapo-coolant sprays are used commonly for pain control. Therapeutic cold is avoided in patients with ischemia, Raynauds Disease, decreased sensation and inability to report pain.

Transcutaneous electrical nerve stimulation (TENS): TENS uses electrical impulses to modulate pain transmission at the dorsal horn via mild electrical stimulation of cutaneous nerve fibers. By varying the current, amplitude, pulse

width and frequency of the electrical signal, patients can achieve analgesia that can last for a few hours after the device is turned off.

Behavioral and psychological treatments: Hospitalized patients spend a majority of time in their beds and rooms alone. It is not uncommon for patients to develop anxiety, depression, and catastrophizing thoughts which in turn negatively affect pain treatment outcomes. There is evidence supporting role of psychological interventions in improving pain, function and quality of life. Behavioral techniques that have a positive impact include mindfulness meditation, progressive muscle relaxation, diaphragmatic breathing and even prayer.

9.3.2 Pharmacological Management

Pharmacological interventions can be initiated and safely titrated in patients with liver failure [2]. There is paucity of research on drug dosing, dosing intervals in this population, and modifications of typical prescribing patterns are recommended. Exercise caution in patients with multi-organ failure. Topical medications such as lidocaine patches, salonpas patches, diclofenac, are preferred due to low risk of systemic toxicity, no need for dose adjustment.

Certain medications turn into an active metabolite that is more potent than the original medication. In the presence of liver failure there will be reduction in the active metabolite with reduction in efficacy of those medications. That is why giving medications that will not undergo live metabolism might be recommended in certain cases.

Codeine is metabolized to Morphine, Hydrocodone is metabolized to Hydromorphone and Oxycodone to Oxymorphone.

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX-1 and COX-2) and release of prostaglandins, prostacyclin, and thromboxanes. Their use is associated with increased risk of gastrointestinal bleeding and nephrotoxicity. There are reports of worsening renal failure in patients with liver cirrhosis with NSAID use [3]. Additionally, NSAIDs use in liver failure can worsen thrombocytopenia, coagulopathy and exacerbate ascites and edema [3].

Recommendation: avoid all NSAIDs

Acetaminophen is a commonly used over-the-counter analgesic and antipyretic. It is metabolized in the liver by CYP-450 into a toxic metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI). Fulminant hepatitis can develop when ingested in doses greater than 10–15 g. A common misconception is acetaminophen should be avoided in patients with liver failure. A study of six patients with chronic liver disease, received 4 g of Acetaminophen for 5 days, without systemic toxicity or hepatotoxicity [4]. Studies have shown that short duration use of acetaminophen in patients with liver cirrhosis is not associated with worsening liver injury [5, 6].

Recommendation: Limit acetaminophen to 2 g/day (including combination medications).

Opioids should be used cautiously in patients with liver failure. Recommendations include avoiding extended release formulations, adjusting dosing and prolonging dosing intervals [7, 8]. Opioids exert their analgesic effect by binding to four different receptors. The distribution of these receptors in the body and different tissue densities account for their varying effects.

Mepridine undergoes extensive metabolism in the liver, and its metabolite normeperidine is neurotoxic, with potential to cause delirium, seizures, and tremors. Meperidine has therefore fallen out of favor. Codeine is a prodrug and is metabolized by the enzyme CYP 2D6 to morphine. Approximately 5–10% Individuals lack this enzyme, and 1–2% are ultrarapid metabolizers. Codeine is not recommended due to its reduced and varying analgesic effects. Fentanyl is generally safe to administer in this patient population once a total daily opioid requirement is calculated.

Morphine undergoes glucuronidation in the liver, which is usually preserved in patients with liver failure [8, 9]. Multiple studies have reported delayed clearance of morphine by 35–60% in patients with cirrhosis [7–9]. Bioavailability of oral morphine is increased due to decreased first pass metabolism. Hence, morphine dose should be reduced, especially in patients with concomitant renal failure. To avoid accumulation of toxic metabolites, a twofold increase in dosing interval is recommended [5, 9]. Accumulation of hydrophilic metabolites can result in seizures, respiratory depression and hepatic encephalopathy. Morphine should be avoided in presence of renal failure.

Recommended starting dose: 5 mg q 6 h

Tramadol undergoes hepatic oxidation, thus may have unpredictable effects in liver failure. However, there have been reports of successful management of pain in patients with liver cirrhosis when acetaminophen was not effective [5]. Caution is advised in patients with history of seizures.

Recommended starting dose: 50 mg q 12 h.

Oxycodone and hydrocodone is metabolized in the liver and excreted by the kidneys. Peak plasma concentration and half-life of oxycodone is increased in patients with liver failure. Reduce the dose and increase the intervals between subsequent dosing for these two drugs.

Recommendation: Hydrocodone 5 mg q 6 h; Oxyocodone 5 mg q 6 h.

Hydromorphone is similar to morphine in regards to its metabolism in the liver and excretion thorough the kidneys. It is estimated to be 5–7x as potent as morphine. Thus similar dose reduction and prolonged interval of administration is recommended. Due to the low levels of its primary metabolite (hydromorphone-3-glucuronide) which is excreted by the kidneys, it is the drug of first choice in patients with concomitant renal failure.

Recommended starting dose: Hydromorphone 1 mg q 6 h (first choice in concomitant renal failure).

Methadone undergoes hepatic metabolism and biphasic elimination. The A-elimination phase lasts 8–12 h and equates to the period of analgesia. The B-elimination phase ranges from 30 to 60 h which is insufficient for analgesia, but sufficient to prevent opioid withdrawal. In the short term, methadone is safe in liver failure patients, even those with renal impairment. Methadone is not recommended

in opioid naive patients or as a new medication in opioid sensitive patients during hospitalization. It is however safe to continue methadone if a patient already taking methadone as an outpatient, is hospitalized with liver failure. If a decision is made to prescribe methadone for inpatient use, it is advised to start at 2.5 mg q 8 h. An EKG must be obtained prior to initiation and a follow up EKG within 3 days after titration to monitor for QTc prolongation (increased risk if QTc > 450 ms, contraindicated if QTc > 500 ms).

Recommendation: avoid use if patient is not currently on methadone. Continue outpatient dose while in hospital—may break up into TID dosing for additional pain control but will need to return to once daily dosing on discharge.

Often times, patients with liver failure experience neuropathic pain from nutritional deficiencies, metabolic abnormalities, alcoholism and diabetes [5]. Antidepressants and anticonvulsants can be used to help achieve additional analgesia. Serotonin-norepinephrine reuptake inhibitors (duloxetine) have a black box warning of drug-induced liver injury and therefore must not be prescribed in liver failure.

Tricyclic antidepressants (TCAs) have been proven to be effective in treating neuropathic pain. Their mechanism of action is attributed to the inhibitory effects on the reuptake of serotonin and norepinephrine in bulbo-spinal neurons and enhanced descending inhibitory serotonergic and noradrenergic controls from the brain to the dorsal horn. TCAs are metabolized primarily by the CYP-450 (CYP2G6) system and excreted by the kidneys. TCAs have dose-related anticholinergic and cardiovascular side effects. Nortriptyline and desipramine have reduced potency, less sedative side effects are preferred TCAs [5].

Recommendation: Start at 10 mg qhs with a slow titration 50 mg qhs as needed

Gabapentin and Pregabalin are anticonvulsant drugs that are the mainstay in the treatment of neuropathic pain. They bind to the alpha-2-delta subunit of voltage gated calcium channels, reduce calcium-dependent release of excitatory neurotransmitters and decrease neuronal hyperexcitability. They are excreted by the kidneys and do not typically require dose adjustment in liver failure. Their use is limited by their side effects such as sedation, ataxia, dizziness.

Recommendation: Gabapentin is first line drug, start at 300 mg daily with slow titration over weeks. Avoid if CrCl <30. Pregabalin is started at 50 mg BID, slowly titrated over weeks. Monitor for side effects.

9.4 Interventional Treatment

In addition to oral analgesics and conservative management, there are several interventional techniques to improve pain control and decrease consumption of opiates and other analgesics. Regional nerve blocks, joint injections, epidural and soft tissue injections may be an effective pain management option in those who are unable to tolerate oral medications due to medical comorbidities or adverse effects from medications. Patients with liver disease may have increased risk of bleeding which

makes interventional procedures risky or contraindicated. It is important to check liver function tests and coagulation profile to determine the risk of bleeding before proceeding with an intervention.

9.5 Pain Assessment Tools

– Numerical Rating Scale—sensitivity to treatments (strength), weakness—no ratio qualities. ex: difference between 1 and 3 is not equivalent to 7–9 on a 0–10 scale
– Visual Analog Scale—sensitive to treatment effects, correlates with pain behaviors, ratio-level scoring properties. Weakness—can be tedious as a ruler is needed to measure the score, difficult to use in patients with cognitive deficits (high non completion rate)
– In cognitively impaired patients, verbal rating scale may be more appropriate.
– Intubated patients, behavioral pain scale (not reliable)

9.6 Discharge Plan for Pain Management

- Avoid NSAIDs
- Recommend acupuncture, heat/cold modalities, progressive muscle relaxation, distraction, mindfulness meditation
- Acetaminophen <2 g/daily
- Continue short acting pain medications, may need to utilize a risk assessment for potential for abuse
- Refer to a pain specialist for consideration of comprehensive multidisciplinary pain management including interventional pain management
- Treat anxiety and depression. Consider referral to a pain psychologist

9.7 Summary

- Patients with liver failure can use analgesics with appropriate dose adjustments and prolonged dosing intervals. Titrate cautiously.
- Consider non-pharmacologic treatments such as topical cold & heat, massage, relaxation, music therapy, breathing exercises, mindfulness meditation
- Use topical medications whenever feasible and appropriate, e.g. local joint pain, nerve pain
- Do not use oral NSAIDs, Meperidine, codeine
- It is safe to use acetaminophen in doses <2 g/day

- Explore feasibility of regional analgesia prior to starting oral medications, including opioids
- When prescribing opioids, recommend short acting/IR opioids with extended dosing intervals. Hydromorphone is preferred over Morphine in patients with concomitant renal impairment
- Avoid long acting opioids
- check risk of bleeding before planning an interventional pain procedure

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Chapter 10
Patient with Renal Failure

Raj Desai and Nalini Sehgal

10.1 Introduction and Pathophysiology

Pain is commonly reported by patients with chronic kidney disease (CKD), >58% CKD patients experience pain, and 49% have moderate to severe pain [1]. Pain is predominantly of musculoskeletal origin, although neuropathic and mixed nociceptive/neuropathic pain conditions are not uncommon. Pain assessment and treatment in CKD is suboptimal and there are no evidence based guidelines for treatment of pain in CKD. Despite the efficacy of acetaminophen, its use is extremely low, NSAID use is inappropriately high, opioid use and selection of opioid is inappropriate in CKD.

There are many challenges to pain treatment in CKD: increased risk for adverse effects from associated comorbidities, increased drug sensitivity, a small margin between analgesia and toxicity, drug and metabolite accumulation due to impaired excretion, altered drug pharmacokinetics and pharmacodynamics. There is limited data on analgesic pharmacokinetics, level of evidence for use of individual analgesics varies considerably, most studies are small, single dose studies, or short duration studies and data on clinically important outcomes is lacking [1, 2].

The scope of this chapter is to discuss commonly utilized pain treatments that are safe in patients with CKD including end stage renal disease (ESRD). CKD is defined as a GFR <60 mL/min/1.73 m^2 for 3 months or more or structural/functional kidney damage with or without changes in GFR. Based on disease progress, CKD can be divided into five stages: stages 1 and 2 have normal or mild reduction of renal function and GFR, stages 3 & 4 are moderate to severe impairment of renal function and reduction in GFR, stage 5 is end-stage renal disease (ESRD). ESRD is defined as GFR < 15 mL/min/1.73 m^2 for greater than 3 months [3].

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10.2 Treatment

A multi-modal pain management approach is strongly recommended to optimize treatment outcomes.

10.2.1 Non-pharmacological Management

These treatment modalities are often similar to the general chronic pain population, and are safe in patients with CKD with little to no adverse effects. Many ESRD patients have limited physical, respiratory, or cardiac functional capacity thus limiting some physical interventions such as physical or occupational therapy (exercise, soft tissue release, massage). Patient participation in physical and occupational therapy at a slower, more tolerable pace is recommended.

Therapeutic heat (hydrocollator packs, fluid baths, heat wraps and ultrasound diathermy) and therapeutic cold (ice packs, ice massage, contrast baths and vapocoolant sprays) are thermal modalities that can decrease pain in CKD/ESRD. Heat therapy improves elasticity of soft tissues, increases local blood flow, metabolic activity, oxygen demand and capillary permeability [4, 5]. Cold therapy leads to vasoconstriction, decreased metabolic activity, decreased enzymatic activity, and decreased oxygen demand [4, 5]. It is best to avoid use of thermal modalities in areas with decreased sensation, ischemia, or in presence of peripheral vascular disease.

Electrical stimulation, using transcutaneous electrical nerve stimulation (TENS), has been employed in pain management for several years, it modulates pain transmission at the dorsal horn. The device consists of skin patches and a wearable device that allows for adjusting the current, amplitude, pulse width and frequency to achieve analgesia that can last for a few hours after turning off the device.

Patients with ESRD experience decreased social interactions, depression, anxiety, catastrophizing and pain related activity interference. Evaluation and treatment for comorbid psychological conditions is therefore recommended. Psychological interventions such as cognitive behavioral therapy, progressive muscle relaxation, mindfulness meditation, music therapy, diaphragmatic breathing have demonstrated efficacy in improving pain catastrophizing, pain interference, depression and anxiety in acute and chronic pain.

10.2.2 Pharmacological Management

Current approach to pain management in CKD is adopted from guidelines on chronic pain management in general population and in geriatric population, supplemented by consensus statements/ expert opinions. There is no study on long term use of any analgesic in CKD.

Acetaminophen: Analgesic of choice for mild to moderate pain, and is one of the safest, most cost-effective non-opioid analgesic when administered in analgesic doses. The mechanism of action is not well understood, it has analgesic and antipyretic effects attributed to inhibition of central prostaglandin synthesis. The drug is metabolized in the liver to inactive metabolites. Less than <5% of the drug is excreted in the urine. Acetaminophen has a half-life of 1–4 h and the half-life is unchanged in CKD. There is no need to reduce the dose [1]. Acetaminophen is removed by hemodialysis.

Recommendation: acetaminophen 500–1000 mg q 4–6 h, with maximum of 4 g/day (2 g if concomitant Liver failure). IV is recommended over PO, if available, for greater analgesia.

Non-Steroidal anti-inflammatory drugs (NSAIDs): NSAIDs primarily inhibit cyclooxygenase (COX-1 and COX-2) and secondarily, inhibit transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. They deplete renal vasodilator prostaglandins, allow unopposed vasoconstriction and decrease renal blood flow. NSAIDs undergo biotransformation in the liver and are excreted by the kidneys. They have been shown to accelerate renal impairment in healthy patients and early CKD patients. A systematic review and meta-analysis of observational studies found no significant risk of accelerated CKD progression with regular NSAID use in patients with stage 3–5 CKD but high dose NSAID use significantly increased risk of accelerated CKD progression [6]. If NSAIDs are used, risks must be balanced against the benefits and use limited to shortest duration possible with close monitoring of renal function. NSAIDs should be avoided in patients with conditions that can impair renal function, such as advanced age, diabetes, use of ACE inhibitors and dehydration or hypotension. COX-2 must also be used cautiously. NSAID may worsen renal function in CKD 3–5 and are not recommended [1, 7].

Recommendation: Utilize lowest effective dose with short acting agents. Topicals are recommended over oral NSAIDs (lowest effective dose).

Opioids: Analgesic of choice in patients with moderate to severe pain. Codeine, Morphine, and Meperidine are contraindicated in patients with ESRD. They have toxic metabolites that are renally excreted and their accumulation in CKD causes hyperalgesia, neurotoxicity, respiratory depression, and other unwanted side effects.

*Medications that should **absolutely** be avoided in patients with renal failure are Codeine, Morphine, Meperidine.*

Tramadol: It has dual mechanism of action: partial μ-agonist activity and serotonin and norepinephrine reuptake inhibition. Tramadol is metabolized by the liver into an active metabolite, O-desmethyltramadol (M1) and 90% of the drug is excreted by the kidneys, 30% unchanged, 60% as a metabolite. Accumulation of M1 metabolite in CKD can cause sedation and seizures. Co-administration of serotonin re-uptake inhibitors and other serotonergic drugs also increases seizure risk. Lowering the maximum daily dose and increasing the interval between doses is advised [7, 8].

Recommendation: Avoid Extended Release (ER) formulation. Tramadol should be dosed q 50–100 q 12 h with a maximum dosage of 100 mg daily with

GFR < 30 mL/. It is significantly removed with hemodialysis, thus administered after hemodialysis.

Oxyocodone: A strong (1.5 times more potent than morphine) opioid receptor agonist with high bioavailability and metabolized by the liver (noroxycodone and oxymorphone) and excreted by the kidneys (10% unchanged).

Recommendation: Use as second line agent, with close monitoring. Avoid extended release formulations.

Fentanyl: A short acting, strong (75–125 times more potent than morphine) opioid receptor agonist that undergoes hepatic metabolism into an inactive metabolite, norfentanyl, and renally excreted (5–10% unchanged). This is a safe medication to administer in patients with ESRD, as it is metabolized into an inactive metabolite.

Recommendation: No change in dosage or dosing intervals recommended.

Hydromorphone: A short acting strong opioid agonist (5–7 times more potent than morphine) that undergoes hepatic metabolism into an active metabolite (hydromorphone-3-glucuronide, H3G) and is excreted by the kidneys. H3G lacks analgesic properties but possess potent neuroexcitatory properties that are 10 times stronger than the parent compound and can cause allodynia, myoclonus and seizures. H3G concentration is dose dependent but is produced in small quantities by the liver. H3G has been shown to clear with hemodialysis [9, 10].

Recommendation: No change in dosage or dosing intervals recommended.

Methadone: A long acting NMDA-antagonist, serotonin-norepinephrine reuptake inhibitor and opioid receptor agonist that undergoes hepatic metabolism into inactive metabolites and is excreted in the feces (20%). Renal excretion rate changes with pH of urine. There is evidence to suggest that compensatory fecal excretion of methadone metabolites occurs in patients with reduced kidney clearance [8]. It does not accumulate in ESRD and is not filtered appreciably during hemodialysis. Methadone can be effective for neuropathic pain in ESRD patients.

Recommendation: No change in dosage or dosing intervals recommended.

Buprenorphine: A long acting opioid receptor agonist with a ceiling effect for respiratory depression, but no ceiling for analgesia. Buprenorphine is metabolized by the liver into an active metabolite (norbuprenorphine, 10–20%) and minimally excreted by the kidneys. Norbuprenorphine has less analgesic potency and greater potency for respiratory depression but does not cross the blood brain barrier. It is not hemodialyzed.

Recommendation: No change in dosage or dosing intervals recommended.

10.2.3 Adjuvant and Other Analgesics

Gabapentinoids: Gabapentin and Pregabalin are chemical analogues of GABA neurotransmitter and bind to the alpha-2-delta protein subunit of the calcium channels in the CNS. Both medications are renally excreted (92–100%), and have prolonged half-life in CKD patients. These drugs freely cross the blood brain barrier and the dose must be adjusted based on GFR [1]. The drug is removed through hemodialysis.

Recommendation: A dose reduction is recommended. The dose for gabapentin is 300 mg daily, and for Pregabalin 75 mg daily. It can take up to 2 months at these doses to notice an effect.

Duloxetine: A serotonin and norepinephrine reuptake inhibitor. It is not recommended in patients with ESRD. Some have recommended starting at a low dose with a maximum of 30 mg daily [11].

Tricyclic antidepressants (TCA): Primarily serotonin and norepinephrine reuptake inhibitors with adrenergic, antihistaminic and anticholinergic activity. TCAs are metabolized in the liver and excreted by the kidneys. This class of drugs has dose-related cardiovascular and anticholinergic effects, which limits their use in CKD.

Recommendation: No dose reduction needed, but advise to start at the lowest possible dose (Amitriptyline 10 mg). Can take up to 6 weeks to take effect.

10.3 Interventions

Interventional techniques: Regional blocks, joint injections, nerve blocks, epidural injections with local anesthetics and corticosteroids are safe in patients with CKD including ESRD. Reduce local anesthetic dose during interventional procedures (lidocaine, bupivacaine, and levobupivacaine). Extreme caution with minimal dose possible is advised when using low osmolar contrast medium.

Recommendation: Dose reduction recommended with the use of local anesthetics (lidocaine, bupivacaine, and levobupivacaine) and contrast medium.

10.4 Pain Assessment Tools

There are numerous validated pain assessment tools that can be employed to assess pain in CKD patients. Numeric pain rating scale (0–10) is a single item validated pain scale that is common, easy to use and reliable. Single item pain scales do not measure the complexity of pain experience, other multi-dimensional pain scales are available. Where feasible, two scales can be utilized to assess pain in patients with CKD:

1. Edmonton Symptom Assessment System Revised: Renal (ESAS-r:Renal) .
2. Palliative Care Outcome Scale-Renal.

10.5 Management of Pain in the Inpatient Setting

- Modalities and Medications to avoid
  - Avoid therapeutic heat/cold and electrical stimulation over areas of decreased sensation, in patients with peripheral vascular disease and local ischemia

  - Avoid codeine, morphine, dextropropoxyphene and pethidine in CKD
  - Avoid NSAIDs if possible in CKD.
- Safe modalities and medications
  - Physical and Occupational therapy
  - Cognitive behavioral therapy (CBT), Mindfulness meditation (MM)
  - Acetaminophen
  - Medications for neuropathic pain: Ketamine, gabapentin/pregabalin (reduce dose)
  - Opioids: fentanyl, methadone, hydromorphone, buprenorphine.

10.6 Discharge Plan for Pain Management

- Utilize complementary alternative medicine techniques (acupuncture, heat/cold modalities, progressive muscle relaxation, distraction)
- Referral to a pain psychologist, encourage mindfulness meditation.
- Utilize injections/ interventional pain management approaches where indicated
- Pharmacotherapy
  - Start with Acetaminophen <4 g/daily (2 g if concomitant hepatic failure)
  - Avoid NSAIDs, where cannot avoid use, select short acting NSAID at lowest possible dose
  - Before prescribing opioids, assess risk for abuse. Risk assessment tools such as SOAP-R or DIRE may be used.
  - Opioids that are safe to use: fentanyl, methadone, buprenorphine with close monitoring
  - Gabapentin 300 mg daily or Pregabalin 75 mg daily
  - Amitriptyline 10 mg daily with slow titration

10.7 Summary

- Start with therapeutic heat/cold, electrical stimulation and encourage psychological techniques such as relaxation, distraction, and mindfulness meditation
- Complementary and alternative medicine (CAM) treatments are useful as an adjunct to pharmacological or interventional techniques
- Determine if pain is nociceptive or neuropathic and select medications appropriately
- Interventional pain techniques such as regional anesthesia, joint injections, epidural injections where indicated can reduce the need for opioids and other analgesics and provide more localized analgesia without systemic side effects.

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Chapter 11
Patient with Lung Transplant

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11.1 Introduction

Since the first successful lung transplant performed in 1981, the procedure has become a common surgical operation performed for end-stage respiratory diseases in select patients (Fig. 11.1). The indications for lung transplantation have expanded to include not only the two most common indications of idiopathic pulmonary fibrosis (IPF) and Chronic Obstructive Pulmonary Disease (COPD), but also cystic fibrosis, alpha-1-antitrypsin deficiency emphysema, primary pulmonary hypertension and sarcoidosis. In 2017, 2478 lung transplants were performed in the USA. National lung transplant rates have continued to consistently increase, with a transplant rate of 173.2 per 100 waitlist-years in the year 2017, compared to 106 per 100 waitlist-years in the year 2012 [1, 2]. Advancements in perioperative care are largely owed to improved organ preservation, surgical techniques, mechanical ventilation strategies, extracorporeal support and immunosuppressive regimens [3, 4]. Physical rehabilitation and appropriate pain control are essential components of management, best handled with a comprehensive multidisciplinary and multimodal approach.

Postoperative pain associated with thoracotomy and lung transplantation is associated with prolonged mechanical ventilation, increased hospital length of stay, and elevated risk of atelectasis, infections and development of chronic pain and depression [5–8]. A study of 143 patients awaiting transplant reported a preoperative prevalence of pain of 59% [9]. These findings underscore the importance of determining and addressing risk factors for postoperative pain. Another study of 96 lung

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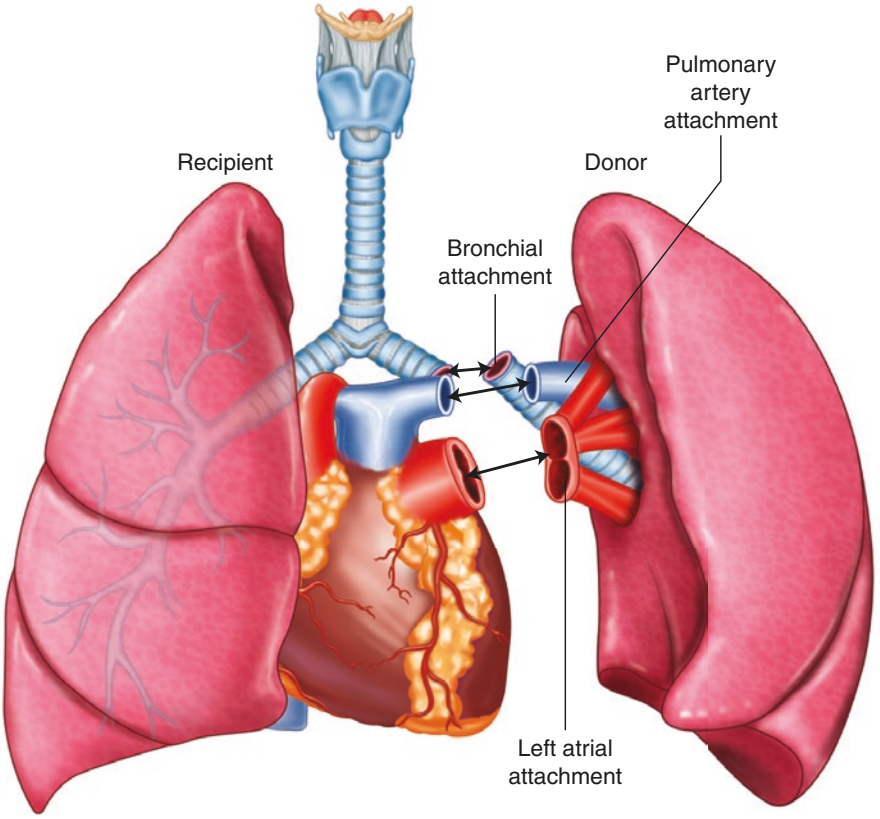

Fig. 11.1 Lung transplant procedure

transplanted patients reported a 49% incidence of pain greater than 3 months after the operation [8]. In a study by Forsberg et al. of 113 lung transplant recipients, the prevalence of chronic postoperative bodily pain was 51% after 1 year, 68% after 2 years, 69.5% after 3 years, 75% after 4 years and 54.5% after 5 years [10].

These patients experience significant psychological stressors during the perioperative period and pain associated with psychiatric comorbidities. Lung transplantation presents unique challenges for the pain management physician. Pain control begins in the preoperative period for many patients with chronic lung disease. Sound inpatient postoperative analgesia is of paramount importance for positive rehabilitative outcomes.

11.2 Pathophysiology

During postoperative hospitalization, lung transplant recipients typically describe pain experienced in the chest, back, neck or shoulders. Work of breathing may be increased chronically and/or during exacerbations of disease states as part of a

physiological response to compensation for hypercarbia or hypoxemia. The same is true during the postoperative recovery should any of these acid-base perturbations occur. During these periods, there is increased use of accessory muscles of respiration including the scalene, sternocleidomastoid, intercostal, erector spinae muscles and the diaphragm. The rectus abdominis, internal and external obliques and transversus abdominis are also recruited in active labored respiration and in more extreme cases may become fatigued. Overuse of these skeletal muscles may contribute to musculoskeletal pain of the neck, chest and abdomen. Furthermore, it is important to avoid bronchoconstriction in the postoperative period as this leads to hyperinflation and limited lengthening of inspiratory muscle fibers. The muscles are, in turn, less effective during contraction and a greater motor force is required to perform the same mechanical work [12].

Chronic cough and pleurisy are often experienced with recurrent pneumonias, emphysematous disease and chronic bronchitis, and may lead to pleuritic chest pain. This pain may be experienced at the site of pleural inflammation or referred to the neck or shoulder. Headaches can occur secondary to chronic hypoxemia and are often poorly localized, global and achy in nature. The sensation of 'chest tightness' is sometimes perceived as painful. This sensation can occur during periods of airway narrowing due to inflammation, pulmonary edema and bronchospasm. Pulmonary embolism and myocardial ischemia are important perioperative considerations to rule out when any of the above symptoms present.

Surgical site pain is a primary consideration for planning for analgesia. Soft and bony tissues are disrupted by direct incision, blunt dissection, retraction and placement of chest drains. For a single lung transplant procedure, the classical surgical approach is via a posterolateral thoracotomy in the fourth or fifth intercostal space. The posterior arc of the sixth rib is divided, after which a rib spreader is used to open the chest wall. At the end of the procedure, two large-bore chest tubes are left in the pleural cavity and one in the mediastinum. In patients undergoing a bilateral lung transplant, a much more extensive transverse or 'clamshell' bilateral thoracosternotomy is made in the sub-mammary region at the level of T4. The sternum is divided transversely at this level and closed with wires. Two chest tubes remain on each side and an optional mediastinal drain. The intercostal space at which the chest tubes are inserted varies. Patients often complain of pain and soreness at the insertion sites [13]. The innervation from to the affected dermatomes is from the afferent fibers of the dorsal roots of the respective spinal nerves.

11.3 Risk Factors

Several studies have been conducted to assess risk factors for pain in lung transplant patients. Debilitating end-stage pulmonary diseases are associated with chronic pain and it is helpful to differentiate this from acute complaints. For example, a single lung transplant may be performed in a patient who has bilateral pulmonary pathology and the patient may continue to experience the same pain related to the

medical diagnosis, in addition to post-surgical pain. Postoperatively, patients typically describe back pain experienced in the chest, back, neck or shoulders.

In a study by Jacques et al., the independent risk factors of cystic fibrosis, female sex and depression are correlated with a higher preoperative pain score [9]. A preoperative diagnosis of COPD is a risk factor for persistent pain several years after the operation [11]. The presence of pulmonary emphysema was found to be an independent predictor of prolonged postoperative pain in a study by Girard et al. In the same study, 49% of 96 lung transplant recipients reported persistent pain after 3 months. These were more likely to be those who had undergone single lung transplants [8].

A retrospective study found that lung transplant recipients reported higher levels of postoperative pain than those who underwent thoracotomies for other indications [13]. The thoracotomy incision for single lung transplant operations is similar to that for other operations, so it is likely that other factors come into play. A possible contributor includes the long duration of surgery and of soft tissue and rib retraction, although this has not been studied. Of note, the clamshell incision is a more painful incision than a vertical sternotomy performed for bilateral lung transplants [14].

During the postoperative hospitalization, predictors of higher pain levels include pretransplant history of anxiety or depression, bilateral lung transplant and lower six-minute walk distance [15]. Preexisting chronic pain is also a major risk factor for postoperative pain [16].

11.4 Diagnosis

The location of pain related to lung transplant surgery is usually at the surgical site or anywhere in the chest, back or upper abdomen. Pain may be referred to the shoulder, neck, jaw or upper limb. The diagnosis of the source of pain may be obvious or may require further investigation. The patient may present with the sensation of shortness of breath (SOB) or be observed to exhibit increased work of breathing or poor synchrony with the ventilator. The patient may be experiencing pain at the surgical site or chest tube site, which may be superficial or deeper visceral pain. SOB may be accompanied by fever, cough and increased oxygen requirements in the setting of a pneumonia, in which case the pain may be pleuritic in nature. Pain may be related to pleural irritation associated with a pneumothorax, pleural effusion or pneumomediastinum, all potential complications of the surgery. In all these cases, specific associated symptoms and with varying acuity, narrow the differential diagnosis and a plain radiograph of the chest may be diagnostic. Computer tomography (CT) scan, magnetic resonance imaging (MRI) or bedside ultrasound may all be useful tools to help narrow the pain differential diagnosis. Other signs of pain include tachycardia, hypertension and splinting with excessive use of abdominal muscles during respiration. It is important to rule out life-threatening differential diagnosis which may present with chest or back pain. These include acute coronary syndromes, acute pulmonary embolism, aortic dissection and cardiac tamponade.

When chronic pain occurs and the source is difficult to diagnose, electromyography (EMG) is useful to diagnose neuromuscular disorders which may have developed secondary to nerve injury or muscular injury. It provides reliable and reproducible information on nerve dysfunction, muscle dysfunction or abnormal signaling at the neuromuscular junction.

11.5 Treatment

As previously mentioned, treatment should be approached in a wholistic and multimodal manner. A cohesive multidisciplinary team approach involves the surgeon, anesthesiologist, pulmonologist, physiotherapist, psychiatrist and pain management physician. This discussion of management will be divided in to non-pharmacological, pharmacological, interventional and other modalities of care.

11.5.1 Non-pharmacological Management

The non-pharmacological treatment of pain involves several conventional and alternative interventions.

Physical therapy focuses on pulmonary care and is administered in increasing increments as the patient recovers. It typically involves chest vibratory physiotherapy, incentive spirometry and other deep breathing exercises, walking and other forms of cardiovascular exercise, stretching and muscle toning exercises and desensitization.

Medical education and psychologic conditioning help set the atmosphere for appropriate expectations and interpretation of sensory stimuli. Application of these entities early in the course of care also helps reduce anxiety and psychological stress associated with major surgery, which in themselves can distort the perception of stimuli.

Alternative therapies include comfort therapies such as massage therapy, application of heat/cold to affected areas, music or art therapy, yoga and medication. Others include medical hypnosis and acupressure.

11.5.2 Pharmacological Management

The pharmacological treatment of pain after lung transplant is geared toward addressing the regions and factors contributing to the sensation of pain described earlier. This discussion does not provide an exhaustive list but rather a review of the common medications used.

Dexmedetomidine is a selective alpha-2-adrenergic receptor agonist. Dexmedetomidine infusions in the immediate postoperative period facilitate smooth emergence from anesthesia and may be combined with other medications or used independently for the treatment of pain.

Ketamine exerts effects at *N*-methyl-D-aspartate (NMDA), opioid, muscarinic and monoaminergic receptors. In sub-anesthetic doses, it can be used in the immediate postoperative period as a continuous infusion for sedative and potent analgesic properties. Administration of intravenous ketamine facilitates weaning of opioids and other sedatives. Ketamine possesses bronchodilator properties, which may be beneficial in this setting. The drug is however a sympathomimetic and must be used with caution in patients with ischemic heart disease, hypertensive crises and acute psychiatric disturbances.

Opioids are valuable in the acute post-operative period and are usually administered intravenously. Choices of delivery include the use of scheduled 'around the clock' dosing, 'as needed' nurse-administered bolus dosing and patient controlled analgesia (PCA) pumps. The choice of opioid depends on the stage of recovery, comorbidities and desired secondary effects. Remifentanil is very potent and has a short context-sensitive half-life (CSHL), so it does not delay ventilatory weaning. A Remifentanil infusion may be used immediately postoperatively. Hyperalgesia may occur upon its discontinuation and the need for rescue therapies should be anticipated. Hydromorphone, morphine or fentanyl are used for intravenous bolus dosing for analgesia during hospitalization. These medications may also be used as continuous infusions and provide the additional benefit of sedation. The CSHL of fentanyl is longer than that of remifentanil but much shorter than that of morphine. Morphine should be used cautiously and at a reduced dose in patients with renal failure. Morphine-6-glucoronide (M6G) is an active metabolite with mu-receptor agonist effects more potent than morphine. It can accumulate to toxic levels, especially in the setting of renal failure [17]. In addition to its analgesic effect at mu receptors, morphine has proven useful in patients to reduce breathlessness or "air hunger", which in turn lends to a reduction in respiratory rate, hyperinflation and anxiety [18]. Orally administered oxycodone and morphine are useful especially when transitioning a patient from parenteral analgesic to an oral regimen. The medications are available in immediate and extended release formulations. Opioids are a potent and valuable class of drugs for use in the immediate postoperative period. Their prolonged use is associated with tolerance and predisposition to opioid-use disorder [19]. Additionally, it is important to consider whether a patient is opioid naive or tolerant when planning an analgesic regimen. In a 2018 retrospective study for lung transplant recipients, it was found that a history of pretransplant opioid use reduces early survival and increases opioid requirements postoperatively [20].

Non-steroidal anti-inflammatory drugs (NSAIDs) must be used cautiously, if at all.

Non-selective NSAIDs exhibit anti-prostaglandin effects which reduce inflammation and pain. However, in this setting, interaction with immunosuppressant medications limits their usefulness, given an increased risk for gastric ulceration, platelet dysfunction and nephrotoxicity.

Acetaminophen is useful and may be administered as intravenous or oral formulation. There is no clinically significant difference in efficacy between the two forms [21]. The medication is generally safe for use without adverse effects or interactions with immunosuppressive medications. Administration should be avoided in patients with severe hepatic impairment, acute hepatitis or severe renal failure. Oral acetaminophen is commonly prescribed on an "as needed" regimen upon discharge from the hospital.

Gabapentinoids are a-2-delta calcium channel ligands derived from gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. These drugs, such as gabapentin and pregabalin, are voltage-gated calcium channel antagonists and have few interactions with other drugs. Pregabalin also has anxiolytic effects. Studies have shown the usefulness of gabapentinoid use in combination with morphine for effective analgesia [22]. Side effects of somnolence and dizziness are not uncommon but may be minimized by starting at low doses and titrating to effect.

11.5.3 Interventions

Other analgesic interventions include regional anesthetic techniques. Both neuraxial and peripheral anesthesia are useful as single-shot techniques, or placement of indwelling catheters for bolus or continuous infusions for prolonged pain relief. Thoracic epidurals provide analgesia for several contiguous vertebral levels. The epidural space is usually entered at the same vertebral level as the surgical incision and the procedure may be performed before or after the operation. In a 2018 study of patients undergoing bilateral lung transplant via bilateral anterior thoracosternotomy, preoperative placement of a thoracic epidural improved analgesia without increasing morbidity, when compared to postoperative epidural placement [23]. In this case, there is no delay between conclusion of the surgery and initiation of neuraxial anesthesia. In fact, use may begin intraoperatively to facilitate smoother emergence from anesthesia and ventilator weaning. For epidural infusions, local anesthetics such as bupivacaine, ropivacaine and lidocaine may be used alone or with adjuncts such as fentanyl, morphine or clonidine.

Paravertebral blocks are an alternative to epidurals and may be unilateral for single lung transplants or placed bilaterally for bilateral thoracotomy. They may also be used to facilitate pain control as part of ventilator weaning towards extubation.

Serratus anterior regional nerve blocks provide analgesia to a smaller area, beneficial for pain at the chest tube insertion sites. The rhomboid intercostal and subserratus plane (RISS) block was recently described [24]. Sub-serratus blocks involve deposition of local anesthetic between the serratus anterior and the external intercostal at the level of desired analgesia. Rhomboid intercostal blocks involve injections between the rhomboid major muscles and the intercostal muscles. Combined, these block the lateral cutaneous branches of the intercostal nerves [24].

Lung transplant recipients are routinely placed on a prophylactic anticoagulation regimen postoperatively. Additionally, patients may be on therapeutic anticoagulation for other indications. It is important to familiarize oneself with the regimen. The use of anticoagulant medications may preclude the use of neuraxial and other regional techniques.

To ensure safe execution of any postoperative neuraxial or other regional techniques, the patient should ideally be awake, oriented and able to follow commands although performance of such techniques in the sedated patient has been described. Subcutaneous deposition of local anesthetic directly at incision sites may be performed at the conclusion of surgery and repeated during hospitalization as a temporizing measure for acute pain before a more definitive intervention.

In the event of development of chronic pain, nerve ablation interventions may be performed in the outpatient setting. These are percutaneous ultrasound-guided procedures. Chemical neurolysis involves destruction of peripheral nerve tissue, such as by injection of phenol, after which distal signal transmission is permanently interrupted. Cryoneurolysis involves insertion of a probe and use of low temperatures to reversibly ablate the nerve responsible for pain transmission. Analgesia may last for several weeks following one application.

11.5.4 Other Modalities

Pulmonary toilette and hygiene are integral components of postoperative care. Addressing weakness, soreness, clearing of airway secretions, muscle spasms and retraining for deep breathing exercises, physiotherapy helps reduce the pain, discomfort and complications associated with limited mobility, pleural irritation and chronic cough. Conversely, pain must be adequately controlled to facilitate meaningful participation in physiotherapeutic care. Chest physiotherapy and the more contemporary high-frequency chest wall oscillation (HFCWO) are routine. Chest physiotherapy, although more widely accessible, is labor intensive, user dependent and requires specially trained personnel. HFCWO is an effective and feasible alternative. Therapy sessions for HFCWO are longer and require use of a larger device with electronic selections of pressure and frequency modes. Both interventions result in a decreased pain scores after treatment. There is an overall greater decrease in pain scores with HFCWO. Bilateral lung transplant recipients show significant preference for HFCWO whereas single lung transplant recipients show no preference [25]. Of note, there is a psychological component to overall comfort and satisfactory reduction in pain. Some patients prefer the human element of interaction of traditional chest physiotherapy, whereas other place more emphasis on the consistency and duration of treatment of mechanical HFCWO [25].

Lastly, if the patient presents to the hospital for a complaint other than that related to the transplant, for example pain elsewhere, related to another acute event or diagnosis, the armamentarium available includes the treatments outlined above. Medication precautions based on allergies, renal and hepatic comorbidities, and interactions with immunosuppressive agents must be considered. Additionally,

regional anesthesia may be considered but a relative increase in risk of infection in these immunocompromised patients should be discussed. Interventional techniques should only be used if the risk versus benefit of the intervention is deemed acceptable. In such cases, single shot techniques may be more favorable than placement of indwelling catheters.

11.6 Pain Assessment Tools

Pain is a subjective entity and it may be challenging to ascertain its presence and severity. Numeric and visual pain assessment tools have been developed and are used for assessment of the symptom in general.

It is always helpful when a patient is awake and able to communicate the location, character, referral and aggravating, relieving and associated factors for pain. This will not be the case while the patient remains intubated and sedated and therefore the clinician must anticipate and appropriately preemptively treat pain for lung transplant recipients. Different evaluation tools are necessary during this period.

The Behavioral Pain Scale (BPS) assesses compliance with mechanical ventilation, movement of the upper limbs and facial expression. For each parameter, a minimum score of 1 to a maximum score of 4 is assigned. A total score (out of 12) is tabulated and a sum greater than 6 corresponds with a need for intervention for pain [26]. The Critical Care Pain Observation Tool (CCPOT) evaluates facial expression, body movements, muscle tension and compliance with ventilation (intubated patients) or vocalization (extubated patients). Each parameter is assigned a maximum of 2 points. A total of greater than 2 out of 8 points is both sensitive and specific for the presence of pain [27]. Both of these tools have been validated for the assessment of pain in the critical care setting.

In awake patients with normal mental status, the Numeric Rating Scale (NRS) may be used. It provides a unidimentional measure of intensity of pain. On a scale of 0 (“no pain”) to 10 (“worst imaginable pain”), the patient chooses a whole number which best correlates to the intensity of pain present. This scale is similar in concept to the Visual Analog Scale (VAS) for pain in which there is a horizontal line with no numbers, and one end corresponds to ‘no pain’ and the other the ‘worst imaginable pain’. The patient picks a point along the line which corresponds to the current intensity of pain. The Verbal Rating Scale (VRS) is again similar in that different adjectives describe increasing pain intensities. This is usually a 4–6-point scale and for ease of recording, the adjectives are assigned numbers [28]. These are all subjective measures and minimal pain for one patient may be reported as maximally intense pain by another. The McGill Pain Questionnaire (MPQ) is frequently used in hospital settings for the multidimensional assessment of pain. It is a three-part assessment tool assessing the sensory, affective and evaluative components of pain. The first part consists of a drawing of the human body on which the patient marks the location of the pain, including an indication of whether it is ‘internal’ or ‘external’. The second is assesses verbal descriptors of pain, from which patients may choose from a list of over 70 adjectives. Thirdly, numeric rating of the intensity

of pain is chosen. The MPQ is one of the most extensive pain assessment tools and has proven useful in a variety of painful conditions despite not having been specifically studied for lung transplant recipients [28]. One limitation is that this assessment can be time-consuming, especially for serial use. There exists a 'short-form' version.

11.7 Challenges in Management of Pain While in the Hospital

Challenges to the management of pain will arise and may be multifactorial. Effective communication among all members of the interdisciplinary management team will help mitigate these challenges and ensure optimal management, in the face of limitations.

As previously noted, the presence of systemic renal or hepatic comorbidities may limit the pharmaceutical choices available to the pain management physician. The presence of opioid-use disorders, opioid tolerance and opioid seeking behaviors may limit the use of this class of potent analgesics or may cause increased requirements in the postoperative period. It may be challenging to determine when, and to what degree, a patient is experiencing pain. This history should be carefully elucidated, and adjustments made as necessary, to ensure the patient's safety and comfort. Adjunctive medications such as buprenorphine, methadone and naltrexone may be considered. Counselling and engagement in rehabilitative programs should be offered prior to discharge.

Obesity may predispose to a body habitus unfavorable for regional anesthetic techniques. Large volumes of adipose tissue may obscure the view for interventions performed by ultrasound-guidance. It may also be more technically challenging to palpate bony prominences and other landmarks for neuraxial techniques in these patients.

The presence of bleeding diathesis or iatrogenic predisposition to bleeding increases the risk of hematoma formation, nerve injury and other complications associated with regional techniques. Thrombocytopenia, anemia, uremia, liver failure, renal failure and therapeutic anticoagulation are reasons to consider avoiding these interventions. In unusual cases, anticoagulation may be held, or transfusion of blood products timed with the procedure if the benefit is deemed to outweigh the risk.

Allergies to any class of medication precludes use thereof.

11.8 Management of Pain in the Inpatient Setting

Adequate management of pain in the inpatient setting charts the course for successful management in the long term and is an indicator of improved quality of life. Undertreated acute pain may predispose to development of chronic pain [29], unreasonable expectations and psychiatric disorders.

A multimodal approach to pain management is optimal. In accordance with the World Health Organization's analgesic ladder, acute pain should be managed incrementally, based on the reported intensity. The cause of pain should, if possible, be elicited by history, physical examination and other indicated investigations. Mild pain may be treated with physiotherapy, changes in position and other non-pharmacologic means and acetaminophen. For moderate to severe pain, a single dose or short course of opioids may be added. Only one drug of any one class should be used at a time and a multimodal approach calls for exploitation of the synergistic effects of different classes of drugs. Regional anesthesia should be considered for moderate to severe pain.

Non-pharmacologic interventions such as cognitive behavior therapy, yoga, physical therapy, comfort therapy and neurostimulation can each play an important role in the inpatient setting and their use should not be underestimated. It is important to be familiar with the modalities available at one's institution and the process by which adjunctive services may be accessed. Conversely, the specialists rendering wholistic care should be familiar with specific precautions to be undertaken with lung transplant patients based on their immunosuppressant, pulmonary support and mobility needs. For example, aqua therapy, pet therapy and certain topical therapies are contraindicated in these immunocompromised patients.

11.9 Management of Pain in the Emergency Setting

A lung transplant recipient may present to the emergency department with a complaint of pain, for several reasons. As always, acute life-threatening diseases states should be ruled out by focused history, physical examination and indicated investigations. If a life-threatening emergency exists, the underlying cause should first be addressed and the patient medically stabilized. If feasible, pain management may occur concurrently. In particular, complications related to lung transplant surgery should be considered. These include acute pulmonary embolism and bronchial or vascular anastomotic dehiscence, leading to pneumothorax, pneumomediastinum subcutaneous emphysema or hemorrhage and its sequelae. Pleural effusion, hemothorax, empyema, pneumonia and pericardial effusion and wound infections are differentials to consider. The location, character, chronicity of pain and the time since transplant surgery are key factors to collectively review when determining the most likely differential diagnoses.

Once life-threatening emergencies have been addressed, the management of pain proceeds as appropriate for the intensity and etiology. Rescue oral medications include acetaminophen, NSAIDs and opiates. If poorly-controlled neuropathic pain is diagnosed, such as from intercostal nerve damage, gabapentinoids and anticonvulsants should be administered in the emergency room. An intercostal nerve block may be considered and can be both diagnostic and therapeutic.

After any intervention, the patient should be monitored in the emergency room for some time and reviewed. Provided that there is no other medical indication for

hospital admission and acceptable analgesia is achieved, emergency room physicians may consider discharging the patient with scheduled and breakthrough oral analgesic medications, in tapering doses. Upon discharge, a plan for referral to a pain management physician, for continuity of care, can be discussed with the patient and encouraged.

11.10 Discharge Plan for Pain Management

Pain management may continue in an outpatient setting. A clearly documented medication regimen should be prescribed for discharge and it should be ensured that the patients understand appropriate rescue therapies and modalities and medications to avoid. Periodic follow-up should be scheduled to evaluate the efficacy of treatment regimens, potentially unsafe medication use, side effects of medications and to determine a plan for appropriate weaning of medications. A pain management physician may not need to see the patient during these visits. Acetaminophen and a short course of oral oxycodone may be considered. These should be used 'as needed'. At discharge, it should be stressed to patients that over the counter (OTC) NSAIDs should be avoided unless approved by the surgical team. Caution must be exercised with OTC cold and flu medications as these often contain acetaminophen and when taken in conjunction with prescribed acetaminophen may lead to overdose. Opioids should be prescribed for only a short period, with strict limitations on refills. The patient and his family should be educated on signs and symptoms of opioid overdose and rescue life-saving treatment. Naloxone should be prescribed, especially in patients receiving high dose extended release opioids. In keeping with a wholistic approach to care, patients should continue physiotherapy and other non-pharmacological interventions which were found helpful during the hospitalization. Exercises can be taught and practiced at home for pain management, in addition to participation in instructed sessions.

11.11 Summary

- It is important that providers understand the postoperative analgesic needs of lung transplant recipients, including the typical postoperative course, pros and cons of medication choices, and contraindications to use of certain modalities.
- A multimodal approach should be applied to the inpatient management of pain in lung transplant recipients.
- Pain should be evaluated using validated assessment tools.
- Pain should be appropriately investigated with history, physical examination and investigations as appropriate.
- Use of intravenous medications is important in the immediate postoperative period. Once pain is controlled, transition to oral regimens should be considered early on

- Regional anesthesia, including neuraxial and peripheral techniques, is effective and can provide prolonged analgesia and decrease systemic opioid requirement
- Epidural catheters are commonly placed preoperatively and used early for maximum benefit. Alternatively, paravertebral catheters may be placed
- Oral opioids, gabapentinoids and acetaminophen are useful during de-escalation from intravenous pharmaceuticals.
- Care must be taken to understand the risks, benefits, drug interactions and alternatives for each medication used in this population. Where applicable, this must be communicated to the patient who should be allowed a choice.
- Non-pharmacological management of pain is important to effective analgesia and should be instituted early during the post-operative course.
- Pain should be continually re-evaluated to determine the efficacy of a regimen, presence of adverse effects, need for alternate therapies, changes in drug dosage and the appropriate weaning regimen.
- A multidisciplinary approach to pain management should be undertaken, with clear and continual communication between different members of the team. The treatment plan should be individualized and based on best-practice and evidence-based medicine.

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Chapter 12
Respiratory Failure and Other Respiratory Conditions

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12.1 Introduction

Chronic obstructive pulmonary disease (COPD) and asthma are two of the most common conditions globally, with 300 million people estimated to have COPD and 235 million estimated to have asthma [1, 2]. The prevalence of both of these diseases is increasing worldwide with another 100 million people expected to be diagnosed with asthma by 2025, and COPD predicted to be the leading cause of death by 2025 [3, 4]. Lung cancer, which is the most common malignancy worldwide, accounts for 12.9% of all new cancer diagnoses (1.8 million in 2012) and has a 5 year survival of only 17.8% [5]. Owing to the large patient populations, the economic burden of these diseases is enormous. In 2011, asthma costs rose to $56 billion while in 2010 the yearly cost of COPD was estimated to be $50 billion [6, 7]. Unsurprisingly, the increased cost is correlated with the severity of the illness. An increased score on the Global Initiative for Asthma (GINA) scale (scale utilized to grade the severity of a patient's asthma) correlates with an increased frequency of asthma-associated exacerbations, hospitalizations, and readmissions [8]. A 12 country study, Continuing to Confront COPD International Patient Survey, found that 15% of patients were hospitalized for a COPD exacerbation within the previous 12 months [9]. Despite accounting for less than 10% of exacerbations, severe COPD disproportionately represents 60–70% of all COPD related health care costs [10]. With much of the initial focus and subsequent care in the inpatient setting being on

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managing the exacerbations and the underlying respiratory disease, a common symptom present in these patients often goes unnoticed pain.

The economic burden of these respiratory conditions is extremely high, but even combined they are dwarfed by the costs of untreated pain. In the United States, pain is estimated to cost $560–$635 million dollars when considering the health care costs and lost productivity [11]. Pain is responsible for approximately 40% of all emergency department visits [12]. Patients with acute and chronic pain are more likely to access health care, require hospital admission, and more often have delayed discharge secondary to inadequate control of pain [13–15]. Pain is commonly experienced by patients with respiratory conditions. The prevalence of pain in COPD patients was found to be 32–60%, higher than the general population [16]. Furthermore, regardless of cancer type or stage, 51% of patients experience pain with a higher prevalence (up to 66%) in lung cancer and with advanced disease [17]. Managing pain in these patients can be challenging, especially in the advanced stages or in severe exacerbations which may precipitate respiratory failure and intensive care admissions.

This chapter focuses on the difficulties and special considerations when managing patients admitted with significant pulmonary disease—focusing on the assessment of pain in both the young and elderly, as well as pain in the spontaneously breathing or ventilated patients. The available pharmacological and non-pharmacological treatments will be discussed, as well as possible interventional approaches to pain management in respiratory failure and common respiratory conditions.

12.2 Pathophysiology

12.2.1 Chronic Obstructive Pulmonary Disease

COPD is a progressive disease of the airways caused by an inappropriate inflammatory response. It most commonly occurs secondary to chronic bronchitis, excess secretion of mucus, and chronic emphysema with destruction of airway tissue [18]. The chest is the predominant area individuals with COPD experience pain. The lung parenchyma and visceral pleura, which lines the outer surface of the lung, are generally deemed insensitive to painful stimuli while most of the pain associated with respiratory conditions involves the chest wall, mediastinal structures and parietal pleura, a thin membrane lining the inner thoracic cavity [19].

The exaggerated inflammatory response can lead to local and systemic changes, which contribute to the pain phenomenon of COPD. Pleurisy, inflammation of the parietal pleura, leads to a well localized chest pain worsened with inspiration. Overexpansion of lungs, such as in COPD can stimulate the parietal pleura. The chest wall including the parietal pleura is innervated by the intercostal (T1–T11), sympathetic, and vagal nerves and is densely populated by nociceptors [20]. The chronic inflammatory state leads to the stimulation of remodeling

by cytokines, such as transforming growth factor-beta, and the formation of scars and adhesions between the parietal and visceral pleura with subsequent loss of lung elasticity [21].

Bronchi are continuously being remodeled as well with the formation of fibroblasts which promote fixed airway obstruction and bronchial spasm [22]. Pulmonary neuroendocrine cells (PNECs) line intrapulmonary epithelium and are believed to be activated by mechanical and painful stimuli such as in spasm [23]. Vagal receptors which line the bronchi, including A-delta and C-fiber nociceptors, are also activated by bronchial spasm and free radicals produced within the inflamed bronchi [21].

The phrenic nerve (anterior rami of C3–C5) provides motor supply to the diaphragm and sensory supply to the central diaphragm and subdiaphragmatic peritoneum as well as to the mediastinal pleura and pericardium. The over-expansion of the lungs leads to excursion of the diaphragm and stretching of the phrenic nerve with ensuing neuropathy. Diaphragmatic pain is referred to the ipsilateral tip of the shoulder (Kehr's sign) and may indicate noxious stimuli on either the thoracic or abdominal aspect of the diaphragm [21].

12.2.2 Asthma

Asthma is a chronic inflammatory disorder of the airways with high inter-patient variability causing reversible bronchoconstriction, airway remodeling, hyperresponsiveness, and edema [24]. The chronic inflammatory response is likely triggered due to the interplay of genetics and environmental exposures. Chronic musculoskeletal pain may develop with increased use of primary and accessory respiratory muscles with chronic inflammation and asthma attacks [25]. Patients with asthma may be on prolonged courses of high-dose inhaled corticosteroids and oral systemic corticosteroids, which leads to an increased risk of developing osteoporosis, which in turn can lead to fractures, impaired mobility, and chronic pain [26, 27]. Musculoskeletal pain is common and may be related to postural misalignment and muscle shortening, especially in patients who were diagnosed at a younger age [25].

Guidelines from the National Asthma and Education and Prevention Program provide a step-wise approach to treatment [28]. Primary goals of treatment are to reduce the risk of future asthma attacks or decreases in lung function and reducing functional limitations or impairment. The treatment provided is based on the severity of disease, ranging from intermittent to mild/moderate/severe persistent, as well as the age of the patient. It is further quantified by the extent of impairment (determined by the frequency of nighttime awakenings, activity interference, use of short acting beta-agonists [SABA], and pulmonary function testing) and the number of exacerbations requiring oral systemic corticosteroids [29]. Patients may be prescribed SABAs, long acting beta-agonists, ICS, leukotriene receptor antagonists (montelukast), theophylline, oral systemic corticosteroids and omalizumab. Early intervention can prevent progression of the disease and limit exacerbations and hospital admissions.

12.2.3 Lung Cancer

Lung cancer is one of the most commonly diagnosed cancers globally, with the majority diagnosed in advanced stages and approximately 80% already metastasized leading to a 5-year mortality of 17.6% [5, 28]. The two most common classifications are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with NSCLC accounting for 80% of cases diagnosed [28]. Fifty percent of lung cancer patients experience poorly localized chest wall pain, which can be exacerbated when pleura and bone are involved [30]. Metastases to bone can cause severe pain secondary to lytic processes and periosteal inflammation with intercostal nerve damage [29, 31]. Neuropathic pain involves anomalous somatosensory processes that occur within an inflamed or injured nerve of the central or peripheral nervous system. The syndromes commonly present in lung cancer include radiculopathy, plexopathy and mononeuropathy [32]. Radiculopathy is a manifestation of the compression or inflammation of a nerve root which can occur when lung cancer metastasizes to the vertebrae. Nerve involvement of the upper extremities is common with Pancoast Tumors causing, ipsilateral upper arm neuropathic pain with tumor invasion of the brachial plexus [30]. This malignant brachial plexopathy may present with Horner's Syndrome with the key features of miosis, anhidrosis and ptosis on the affected side as well as eventual seeding of the epidural space as the tumor invades nerve roots.

Pain in advanced cancer affects 66.4% of patients and has significant deleterious effects on quality of life and psychological well-being [17]. Managing the pain will require an ever-evolving regimen as patients progress through treatments and possibly palliative care. The World Health Organization (WHO) analgesia ladder, which was initially developed in 1986 and subsequently updated in 1996 and 2019, serves as a guide for physicians treating cancer pain [33]. Recently there have been advancements in the management of acute and chronic pain that are excluded from the ladder, leading groups to suggest adding a fourth or even fifth step on the ladder as the current ladder fails to treat 10–20% of a cancer patients' pain [34, 35]. The WHO ladder does not currently include advanced interventional pain techniques such as nerve blocks, intrathecal or epidural drug delivery systems, spinal cord or nerve stimulators, or neuro-destructive procedures.

First line treatment for stage I NSCLC is lobectomy with lymph node dissection which can result in post-thoracotomy pain syndrome, characterized by a combination of neuropathic and myofascial pain persisting for months after surgery. Advancements in minimally-invasive and robotic surgeries has reduced the requirement for large open thoracotomy incisions. As opposed to a 5–10 in. incision, surgeons performing video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery require only a limited number of ½–3 in. incisions with minimal mechanical spreading of the ribs.

Common treatment modalities can cause or worsen existing neuropathic pain. Chemotherapeutic agents are often utilized as neo-adjuvants, to shrink tumors prior to surgery, or adjuvants after surgery to eliminate any remaining cancer cells. Vinca

alkaloids, cisplatinum, and paclitaxel can cause painful paresthesias with possible loss of sensation [32]. In the instance of cisplatinum, the dorsal root ganglia (DRG) are targeted with ensuing apoptosis of the DRG and the onset of dysesthesias and sharp, burning pains [36].

Radiation therapy may be employed with multiple sessions over several weeks either prior to surgery or after surgery ± chemotherapy. During radiation therapy, brachial plexopathy may occur from direct injury to the axons and Schwann cells and demyelination of the nerve [32]. It may have a delayed onset of 4–5 months after treatment and affects 1.8–4.9% of patients after radiotherapy. Even more frequently occurring is a delayed brachial plexopathy, which is likely due to fibrosis of the nerve; this may impact 14–73% of patients 3 years after completing treatment [32]. It is important to determine whether the pain is the result of tumor recurrence or radiation therapy. The presence of lymphedema usually indicates radiation-induced plexopathy, while Horner's Syndrome and severe progressive pain suggest neoplastic invasion of the brachial plexus. If either of these symptoms occur, an MRI is essential to determine the etiology [32]. Novel lung cancer therapies carry the potential to cause neuropathic pain. Recent advancements in drug therapies have led to the development of targeted immunotherapies directed towards specific mutations. One such immunotherapy is cetuximab, which inhibits epidermal growth factor receptors. Mouse models and isolated case reports have shown the potential for polyneuropathies or progression of radiation induced plexopathy with this therapy [37, 38].

12.2.4 Respiratory Failure

Respiratory failure is a common and life threatening condition with a mortality rate of 20.6% [39]. Etiology include pneumonia, pulmonary edema (cardiogenic or non-cardiogenic), pulmonary embolism, traumatic chest injury, COPD or asthma exacerbations, airway obstruction, neuromuscular failure or depression, or can be multifactorial [40]. Respiratory failure is a result of the inability for the lung to exchange gases and may have an acute onset or chronic course; most often, respiratory failure is characterized as either **Type I (hypoxemic)** respiratory failure or **Type II (hypercapnic)** respiratory failure. Hypoxemic failure is noted as a PaO_2 of <60 mmHg and a $PaCO_2$ of <50 mmHg while hypercapnic respiratory failure is a PaO_2 of <60 mmHg and a $PaCO_2$ > 50 mmHg [41]. There are five primary pathophysiological processes that can lead to hypoxemia:

1. Low inspired oxygen (i.e. altitude)
2. Hypoventilation (i.e. opioid overdose)
3. Diffusion impairment (i.e. idiopathic pulmonary fibrosis)
4. V/Q mismatch (i.e. pulmonary embolism or pneumonia)
5. Shunt (i.e. atelectasis)

When patients present in respiratory failure the underlying discomfort and pain may not be able to be appropriately assessed until after the acute presentation. The severe

dyspnea, wheezing, or stridor may make limit communication. The hypoxemia and hypercapnia may cause somnolence or confusion with altered mental status. The causes of pain will be similar to the previously discussed pathologies with likely significant parietal pleural inflammation.

The mainstay initial treatment for hypoxemic respiratory failure is supplemental oxygen. There is a multitude of devices to deliver oxygen including nasal cannula, simple mask, non-rebreather masks, high-flow nasal cannula, endotracheal tube, and as a last resort extracorporeal membrane oxygenation (ECMO). Hypercapnic respiratory failure results from an inability to ventilate, therefore non-invasive ventilation like continuous positive airway pressure (CPAP) or mechanical ventilation via an endotracheal tube or tracheostomy is required.

Respiratory failure secondary to pulmonary edema, pneumothorax, or as a complication of thoracic surgery may necessitate the placement of a chest tube. Ongoing pain is common after placement of a chest tube; studies suggest that 50% of patients with actively draining chest tubes rated their pain as a 9–10 out of 10 in severity [42]. The chest tube causes inflammation of the parietal pleura and thoracic fascia [19]. The deep fascia overlying the intercostal muscles and the endothoracic fascia on the inner rib cage are innervated by spinal and sympathetic nerves with nociceptive afferents [21]. Stretching of the intercostal muscles, which occurs with thoracostomy, activates the C-fibers. In patients with chronic pulmonary conditions like COPD with stiffer chest walls there is a lower threshold for activation [21]. The British Thoracic Society Pleural Guidelines 2010 assumed smaller bore chest tubes caused less pain but a prospective analysis published in 2012 found no differences in clinical outcomes or pain experienced by patients between 28–32 and 36–40 French chest tubes [41, 43].

12.3 Diagnosis

The diagnosis of pain related to respiratory conditions can be difficult due to the multitude of conditions that can present with chest pain. Any patient presenting with chest pain must undergo testing that rules out cardiac, musculoskeletal, pulmonary, esophageal, and vascular causes. Clinicians evaluating a patient with chest pain must take a detailed history and perform a thorough physical examination to evaluate the course of presenting symptoms and any previous chronic conditions. Initially, patients will require an electrocardiogram, complete blood count, basic metabolic panel and cardiac enzymes if there is a high suspicion for cardiac etiology [44]. A transthoracic echocardiogram may also be necessary and can aid in identifying other causes of chest pain such as pulmonary embolism, valvular abnormalities, and cardiomyopathies.

Non-cardiac chest pain (NCCP) is defined as recurrent chest pain indistinguishable from ischemic heart pain after a cardiac cause has been excluded [44]. A chest x-ray or CT chest with or without contrast can quickly be performed and identify numerous sources of NCCP such as aortic dissection, pulmonary embolism,

pneumothorax, pleural effusions, rib fractures, and mediastinal or intrathoracic masses. Bedside ultrasound is an invaluable tool in evaluating patients in respiratory distress as it can be used to diagnose conditions such as pulmonary edema and pneumothorax. The Bedside Lung Ultrasound in Emergency (BLUE) protocol was found to have a 90.5% accuracy in diagnosing the cause of severe dyspnea [45]. History suggestive of gastroesophageal reflux disease (heartburn, regurgitation, chronic cough, or sour taste in mouth) can be further worked up with endoscopy, manometry, barium swallow studies, or pH testing [44].

In COPD, patients experience dyspnea, chest tightness, productive cough, decreased exercise tolerance, fatigue, and anxiety. Headaches may occur secondary to chronic hypoxemia, with associated muscle and joint pain occurring in the neck and upper back. On presentation, the patients may be cachectic with significant skeletal muscle wasting and atrophy due to the overuse of accessory respiratory muscles (scalene, sternocleidomastoid and erector spinae muscles). The respiratory and pain symptoms are closely associated with patients describing the pain limiting their ability to breath, which only further exacerbates their dyspnea and subsequent pain [46].

The severity of COPD can be determined by a pulmonary function test (PFT) to measure the forced expiratory volume in 1 s (FEV1) which allows the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria to be applied. Patients with moderate COPD (GOLD 2) were most likely to report pain, while those with severe COPD (GOLD ≥3) were more likely to report respiratory complaints than pain [18, 19]. An arterial blood gas (ABG) provides valuable baseline carbon dioxide and oxygenation. Headaches occur with chronic hypoxemia and hypercapnia [47]. Patients complaining of worsening neck and back pains may require further evaluation with a radiological study such as an x-ray, CT scan or MRI if neuropathy co-exists. Prolonged courses of steroids contribute to osteoporosis in COPD patients, which may result in vertebral compression fractures with neural root involvement [18].

Asthmatics most commonly experience dyspnea, recurrent cough, wheezing, chest tightness and/or difficulty breathing. The symptoms are often precipitated by an inciting event or exposure such as exercise, weather changes, viral illness, allergens, or emotional stress [28]. During an acute exacerbation, audible wheezing is commonly noted with associated cough. The cough is frequently worsened at nighttime, with exertion, or with emotions such as laughing or crying. Accessory muscle use is common and can lead to muscular overuse and strain. Pulmonary function testing may be indicated after a thorough history for patients ≥5 years of age [28]. Spirometry is utilized, which typically measures the FEV_1, FVC, and FEV_1/FVC ratio before and after the use of a bronchodilator, which will reverse the airway narrowing present in asthma. Bronchoprovocation may be necessary if spirometry is normal, but the history and exam are highly suggestive of asthma. Airway hyperresponsiveness triggered by administration of methacholine, cold, exercise or histamine confirms the presence of asthma [28]. Allergy testing may also be indicated for patients with suspected atopic and hypersensitivity conditions such as eczema, asthma, and rhinitis. A peak flow meter can also be utilized to diagnose and

self-monitor asthma by measuring the patient's maximal peak expiratory flow (L/min) and comparing the value to a standardized chart based on age, sex, and height [28].

Potential lung cancers may be identified with chest x-ray and CT requiring further investigations for staging, while the treatment chosen often depends on the histological findings from the biopsy samples. Sputum cytology with bronchoscopy has 99% specificity and 88% sensitivity for central endobronchial lesions, but lacks sensitivity for peripheral lesions [48]. Emergence of endobronchial ultrasound and electromagnetic navigation have aided in improving the sensitivity of flexible bronchoscopy in diagnosing peripheral lung cancers. Transthoracic needle aspiration has a sensitivity of 90% for peripheral lesions and is useful in malignant disease [48]. Metastatic pleural effusion can be diagnosed with pleural fluid cytology which has a sensitivity of 72%, but thoracoscopic pleural biopsy has a diagnostic yield of 95–97% [48]. As mentioned previously in the chapter, diagnosing lung cancer in its early stages yields an improved 5-year mortality and ensures these patients have their cancer pain treated appropriately.

12.4 Treatment

Identifying the specific respiratory disease process can assist in managing painful symptoms since medical management of the underlying respiratory disease can achieve improvement in pain. The treatments discussed in the following section will include pharmacological, non-pharmacological, and interventional techniques that can aid in improving NCCP associated with pulmonary disease. There is no "one size fits all" approach to managing pain in these patient populations. Therefore, incorporating a multi-modal pain regimen would be necessary to achieve improvements in pain and quality of life.

Optimizing COPD treatment for patients has been shown to cause reductions in pain without the use of analgesics or interventional pain techniques [49]. Smoking cessation is a priority for patients started on a combination of inhaled muscarinic antagonists, SABAs and LABAs, and ICS depending on the GOLD classification [50]. Methylxanthines (Theophylline) and PDE-4 inhibitors (Roflumilast) have also shown benefit when used in combination therapies. During an exacerbation a short course of antibiotics and/or oral steroids may be required [22]. Oxygen may be necessary in arterial hypoxemia with a $PaO_2 < 55$ mmHg or $SaO_2 < 88\%$ with a target SaO_2 of >90%. Headaches, which are related to hypoxemia, may benefit from oxygen therapy overnight, as patients most commonly wake up with the headaches [47]. Additionally, acetaminophen and non-steroidal anti-inflammatory (NSAID's) medicines can be utilized if not contraindicated.

The musculoskeletal pain may also benefit from NSAIDs and acetaminophen in combination with a short course of oral opioid medications with extra caution in patients with severe hypercapnia. Some benefit has also been shown with intravenous morphine in reducing breathlessness, dynamic hyperinflation, and dyspnea by

prolonging expiratory time, decreasing respiratory rate and decreasing anxiety [51]. Pulmonary rehabilitation can be initiated while inpatient with beneficial effects in reducing dyspnea, increasing muscle strength and endurance, improved mobility and quality of life, decreased hospital admissions and improved mental health [52].

Patients with asthma may require prolonged courses of high dose ICS as well as oral systemic corticosteroids, thereby increasing the risk of developing osteoporosis, which may lead to fractures, impaired mobility, and chronic pain [26, 27]. Musculoskeletal pain is also common, and may be related to postural misalignment and muscle shortening, especially in patients who were diagnosed with respiratory disease at a younger age [25].

Muscle relaxants such as tizanidine and benzodiazepines have uncertain benefit, but may provide short-term relief (<2 weeks) for non-specific back pain; however, these medications carry a high risk of sedation [53]. Any severe pain may require opioid medications with close monitoring for any side-effects, but they were found to be inferior to NSAIDs and acetaminophen in improving function.

Patients exhibiting neuropathic pain will require anticonvulsant agents, gabapentinoids or carbamazepine, and/or antidepressant medications such as tricyclic antidepressants (TCAs) and serotonin noradrenaline reuptake inhibitors (SNRIs). The Canadian Pain Society consensus statement on management of neuropathic pain recommends TCAs, SNRIs and gabapentinoids as equivalent first line agents that can be cycled if not effective or combined for greater benefit [54]. The gabapentinoids, pregabalin and gabapentin, bind the α-2δ-1 subunits of the pre-synaptic calcium channels inhibiting the release of excitatory neurotransmitters such as substance P and glutamate in nociceptive neurons [55]. Patients most commonly experience somnolence, dizziness, confusion and dry mouth as dose dependent side effects [56]. The TCAs with greatest efficacy are amitriptyline and nortriptyline which function by inhibiting the reuptake of serotonin and noradrenaline. Increased levels of noradrenaline and serotonin potentiate descending inhibitory pathways by inhibiting synaptic transmission between nociceptive neurons and spinothalamic neurons as well as activating interneurons that release inhibitory endogenous opioids or gamma-aminobutyric acid [56]. The primary concern with TCAs is the anticholinergic side effects that include urinary retention, orthostatic hypotension and cardiotoxicity. TCAs block voltage-gated sodium channels which has the beneficial effect of local anesthetic-like properties but contributes to the cardiotoxic effects including widened QRS complexes >100 ms and ventricular dysrhythmias [56]. To reduce the likelihood of cardiotoxicity, TCAs should be limited to a maximum dose of 100 mg per day [54] . SNRIs such as venlafaxine and duloxetine provide benefit through the reuptake inhibition of noradrenaline, with nausea being the most common side effect [54]. Lidocaine 5% patches may also have benefit for patients with well localized neuropathic pain after thoracic incisions. There is no systemic effect with a maximal penetration of 8–10 mm and has shown benefit in patients with neuropathic pain and allodynia and can be worn for 12 h during a 24-h period [56].

Patients that experienced respiratory failure after a traumatic chest injury or post-thoracotomy can benefit from thoracic epidural analgesia (TEA) or paravertebral blocks (PVB) ± a continuous infusion via catheter. TEA infusions can include local

anesthetic only or local anesthetic combined with an opioid. Bupivacaine 0.125% alone has similar analgesic effects and less respiratory depression compared to bupivacaine 0.05% or 0.1% with fentanyl 2–5 μg/mL or hydromorphone 5–10 μg/mL, but is limited by hypotension and motor blockade [57]. The infusion rate can be titrated to balance benefit with side effects, with an additional patient-controlled bolus to improve pain control at physically stimulating times such as dressing changes or physical therapy. TEA reduces vital capacity and FEV_1 15–20% from baseline, but actually reduces the respiratory compromise caused by significant thoracic and abdominal surgeries due to improved analgesia [58]. In patients with asthma and COPD, TEA does not reduce lung function to a greater extent and results in improved bronchial hyperresponsiveness [58].

The thoracic paravertebral space extends from T1 to T12 and contains spinal nerves, white and grey matter rami, intercostal blood vessels, and the sympathetic chain [59]. PVBs have a similar placement success rate as TEAs and have proven beneficial in pain management for post-operative unilateral thoracotomies and rib fractures. It is possible to achieve a dermatomal spread of 1–4 levels in a single paravertebral injection; additional levels can be achieved with multiple injections. An indwelling catheter may be threaded into the paravertebral space to achieve continuous pain control. Ropivacaine is most commonly used and a continuous infusion rate of 0.1 mL/kg/h is recommended [60]. Compared to TEA, paravertebral blocks were found to shorten the length of hospital stay and have a quicker return to baseline spirometry values in patients who underwent thoracotomy [61].

Pain management for mechanically ventilated patients with continuous infusions of IV opioids can provide the additional benefit of providing sedation. Selecting the appropriate opioid depends on the patients' co-morbidities and hepatic and renal function. Fentanyl has less hypotension, but can accumulate with hepatic impairment and has a significant context-sensitive half-time (CSHT) with prolonged infusion that can delay ventilator weaning [62]. Morphine is also an option; however, histamine release can cause hypotension and its active metabolites morphine-6-glucuronide and morphine-3-glucuronide can accumulate in renal failure [62, 63]. For patients that have been on long courses of fentanyl or morphine and have developed tolerance, hydromorphone can be used and is generally safer in renal impairment. However, hydromorphone-3-glucuronide may accumulate and has neuroexcitatory potential. Remifentanil may be used as well, with the benefit of negligible CSHT, but possible hyperalgesia with discontinuation [62].

A multi-modal approach can be utilized to optimize overall pain control. Acetaminophen and NSAIDs come in a variety of formulations facilitating their administration to intubated patients, and oral forms can be crushed and administered via gastric tubes. To reduce the risk of ulcer formation in ventilated patients, ensure a proton pump inhibitor or H2 antagonist is administered when considering NSAIDs.

Ketamine, a N-methyl-D-aspartate antagonist, has proven to be an effective dual analgesic and sedative. Administration of IV ketamine to ICU patients facilitates weaning of concomitant opioids and sedatives, with Garber, et al. finding a

20% relative reduction in fentanyl and propofol 24 h after initiating ketamine [64]. Beyond the analgesic properties, ketamine is a potent bronchodilator with continuous infusion showing benefit as a recue therapy in refractory status asthmaticus [65]. Ketamine is not without its side effects and must be used with caution in patients with ischemic heart disease, hypertensive crisis, and psychosis [66].

Most cancer patients can be successfully managed using the WHO analgesic ladder. Preferentially providing oral formulations and ensuring regular dosing intervals are integral at every step of the ladder. Patients should first be treated with non-opioid analgesics such as acetaminophen and NSAIDs. If pain persists or increases, a "weak opioid" such as codeine can be added. If the patient's pain remains inadequately controlled, the third step on the ladder suggests a "strong opioid" such as hydromorphone, methadone, or fentanyl be added. Throughout the steps of the ladder, the WHO recommends adjuvants be used such as antidepressants (i.e. amitriptyline), anticonvulsants (i.e. carbamazepine), steroids (i.e. dexamethasone), and bisphosphonates (i.e. zoledronate). A PCA infusion may initially be required in patients who are tolerant to opioids or with severe intractable pain. PCA's improve patient satisfaction through greater control and independence in the management of their pain, but close monitoring with pulse oximetry or end tidal CO_2 must be considered. Bisphosphonates, which inhibit osteolytic activity of osteoclasts, have shown analgesic benefit in patients with bone metastases as well as slowing skeletal destruction, while external beam radiation therapy remains the gold standard for resolution of bone pain.

Patients with intractable neuropathic chest wall pain secondary to bone metastases may benefit from an intercostal nerve block, thoracic nerve root block, or a paravertebral block [30]. Using ultrasound at the bedside, these procedures can be easily performed and provide temporary relief as well as proving to be diagnostic for future procedures such as neurolysis, cryoneurolysis or radiofrequency ablation (RFA). The PVB may be preferred because a single injection reaches multiple thoracic root levels and an indwelling catheter can be placed for prolonged pain relief, including after unilateral thoracotomy [30]. Intercostal neurolysis most commonly uses phenol to destroy the nerve and interrupt transmission beyond the lesion, while cryoneurolysis damages the nerve by freezing the nerve [30]. Neurolytic procedures are most commonly performed in outpatient settings, so an interventional pain specialist evaluation can be arranged upon patient discharge.

12.5 Pain Assessment Tools

Pain is an immensely personal and subjective symptom, requiring clinicians to use well validated pain scoring systems when assessing patients. Poor assessment of pain remains one of the major barriers to achieving pain control [67].

In patients without altered mental status, including older adults, the numeric rating scale (NRS) and verbal descriptor scale (VDS) can be used. The NRS has

patients rate their pain on a scale of 0–10, while the VDS is an escalating scale of pain phrases (i.e. "no pain" to "most intense pain imaginable") [68]. For older adults with mild to moderate cognitive impairment, the VDS or the Faces Pain Scale may be utilized. In the instance of altered mental status or severe cognitive impairment, a thorough exam or observation of behavior is necessary.

For patients that have been intubated and are mechanically ventilated the assessment of pain can be difficult. The Behavioral Pain Scale (BPS) and Critical Care Pain Observation Tool (CCPOT) have both been validated in mechanically ventilated patients. BPS looks at facial expression, movement of the extremities and compliance with the ventilator and assigns a 1 (no response) to 4 (full response) score and a total score >6 indicating the need for pain management [69]. The CCPOT evaluates facial expression, body movement, muscle tension, ventilator compliance, and scores each variable 0 (no response) to 2 (full response) with a score >2 out of 8 highly sensitive and specific for pain [70].

Brief Pain Inventory (BPI) provides a well-validated measure of pain experiences over 1 week and how it interferes with daily functioning and has been applied to patients with COPD previously [18]. BPI has been validated for chronic non-malignant pain in adult populations [71]. The BPI allows a more in-depth assessment of the impact pain has on a patient's quality of life and may identify areas where therapies or interventions may prove beneficial.

The musculoskeletal pain that impacts patients with chronic and acute respiratory conditions can be further evaluated by the Extended Aberdeen Back Pain Scale, which consists of 35 questions that reliably evaluates neck, upper back, and lower back pain, and has been applied to COPD [72, 73].

Since the diagnosis of asthma frequently occurs in the pediatric population, assessment tools must be validated in that group. The Visual Analog Scale (VAS) has been well validated from 3 years of age to adult populations. Wong-Baker Faces Pain Rating Scale and the Faces Pain Scale-Revised use cartoon faces depicting increasing pain intensity and has been validated in ages 3–18 years old and 4–16 year old's, respectively [74].

The NRS or the BPI has been incorporated into cancer-specific classification tools that aim to determine pain prognoses. The Edmonton Classification System for Cancer Pain (ECS-CP) was developed as way to guide pain management in advanced cancers and predict responsiveness, especially during admission to palliative care services. There are five categories—mechanism of pain (none, nociceptive, neuropathic), incident pain (present or not), psychological distress (present or not), addictive behavior (present or not), and cognitive function (none, partial or total impairment) [75]. To better predict pain relief in cancer patients, the Cancer Pain Prognostic Scale (CPPS) was created to identify patients early on with inadequate pain control and a poor pain prognosis. CPPS incorporates the worst pain severity (based on NRS), Functional Assessment of Cancer Therapy (FACT-G) well-being, daily opioid dose, and pain characteristics [76]. The scale scores patients on a 0–17 scale, with 17 indicating the best prognosis in achieving ≥80% pain relief within 2 weeks. This assessment tool has not gained widespread adoption and requires further validation.

12.6 Challenges in Management of Pain While in the Hospital

Treatment of pain in respiratory failure and pulmonary conditions present a unique set of challenges; while the under treatment of pain can lead to a myriad of deleterious effects. Historically, medical education has put minimal emphasis on pain management from medical school through residency [15]. This lack of familiarity and comfort with pain management contributes to a reluctance for doctors to prescribe opioids, as well as a fear of the addictive risk and potential liability for any negative outcomes [15]. When acute pain is inadequately managed patients experience a decline in quality of life with an impaired ability to perform activities of daily living and significant sleep disturbances [15].

There are also numerous physiological consequences related to the stress response triggered by under treated pain. The stress response leads to a surge of hormones that promotes weight loss, glucose intolerance, fever, inflammation, and tachypnea [77]. A prolonged inflammatory phase can contribute to the pain induced stress response delaying a patient's recovery and hospital discharge [77]. Protracted inflammation can precipitate further respiratory compromise and respiratory failure. As mentioned above, inflammation is a primary culprit for patients' pleuritic chest pain.

The sympathetic nervous system is also activated by pain which leads to stimulation of the cardiovascular system causing tachycardia, increased oxygen demands, and hypertension [77]. When patients are already hypoxic and oxygen dependent, every measure should be taken to ensure metabolic oxygen demands are kept to a minimum. Sympathetic stimulation also increases smooth muscle sphincter tone and decreases intestinal motility which thereby increases the risks for developing ileus, which must be closely monitored for when patients are on opioid medications [77].

One of the primary concerns of not adequately controlling pain during the acute stage is the progression to chronic pain. The more severe a patient's episode of acute pain the more likely they are to develop chronic pain [15]. A large multi-center observational cohort study investigating pain in survivors of serious illness (including respiratory failure, NSCLC and acute exacerbations of COPD) 2 months and 6 months after hospitalization discovered a strong association between the amount of pain while an inpatient to the severity of pain experienced months later [78].

Patients in respiratory failure may have other co-morbidities that must be accounted for when considering the use of medications and the potential adverse effects on organ systems. Mechanically ventilated patients are three times more likely to experience acute kidney injury, which subsequently delays weaning from the ventilator and increase mortality by 60% [79]. Impaired renal function limits which analgesic medications can be utilized in a multimodal approach. Through prostaglandin-mediated pathways, NSAIDs negatively impact renal function by reducing blood flow to the kidney and by direct cytotoxic effects [80]. Even in young, healthy patients, seven daily doses of NSAIDs a month significantly

increased the risk of acute and chronic kidney dysfunction [80]. Extreme caution should be exercised when considering using NSAIDs for patients who have baseline renal dysfunction or are at risk of developing acute renal impairment. As previously discussed, renal and hepatic impairment also influences the choice of intravenous opioid that can be used in a patient.

Use of acetaminophen and NSAIDs may alleviate musculoskeletal pain associated with asthma. NSAIDs that inhibit cyclooxygenase-1 (COX-1), like aspirin, should be avoided in patients with aspirin-induced asthma (AIA) [81]. Cross-sensitivity with acetaminophen is possible though the reaction is of shorter duration and milder [35]. Highly specific COX-2 inhibitors, such as celecoxib, have been shown to be safely tolerated by patients with AIA [35].

Pulmonary patients are susceptible to the respiratory-depressant effects of opioid medications. Opioids bind μ-receptors on the respiratory centers of the brainstem resulting in cyclic breathing and eventually apnea [82]. The use of opioids is associated with an incidence of major adverse effects related to respiratory depression of less than 0.5%, although studies have shown up to 30% of patients experience a respiratory rate of less than 8 at least once during a 24-h period [83]. Use of an IV-PCA reduces the burden on nursing and increases patient satisfaction but is not associated with decreased opioid consumption or risk of side effects including respiratory depression [84]. The incidence of respiratory depression with IV-PCA is 0.2–0.5%; however, the likelihood is increased if a basal infusion is running with additional patient-controlled boluses [83]. The respiratory rate of these patients should be closely monitored when administering opioids as part of the pain management regimen for signs of bradypnea. Additional monitoring such as end tidal CO_2 ($ETCO_2$), in combination with pulse oximetry, should be considered as studies have shown $ETCO_2$ is more effective than pulse oximetry alone in early detection of respiratory depression [85].

12.7 Management of Pain in the Inpatient Setting

Devising a plan to manage pain in patients with significant respiratory illness can incorporate multiple modalities to achieve adequate pain control. The benefit of multimodal analgesia is that several sites along the nociceptive pathway are targeted in complement [86]. Peri-operative studies incorporating multimodal regimens have shown reduction in post-operative opioid consumption and improvement in VAS pain scores [87, 88]. Patients may be experiencing pain secondary to both neuropathic and inflammatory processes, so an NSAID or gabapentin alone will be inadequate; therefore, an individualized approach is required to ensure the greatest benefit with the lowest likelihood of adverse outcomes. As described earlier in this chapter, there are risks and benefits to all pharmacological and non-pharmacological approaches to pain management and these factors must be considered when creating a plan. Realistic expectations for the clinicians and patients must also be maintained as complete resolution of pain may be impossible. A 30% reduction in pain scores

was shown to significantly improve a patient's pain experience and provides a reasonable goal for pain control [89].

Mild to moderate pain can be managed with non-opioids like NSAIDs and acetaminophen, while opioids can be incorporated for moderate to severe pain [53]. Use of acetaminophen and NSAIDs together or a combination of NSAID and opioid provide improved analgesia than any agent alone due to drug synergism [86]. Neuropathic agents such as amitriptyline, venlafaxine and gabapentin can be incorporated if the patient endorses any symptomatology consistent with neuropathic pain. Patients presenting with pain refractory to conservative treatments may require an intervention such as a TEA or PVB. These techniques have shown significant benefit in conditions that contribute to respiratory failure and can provide a dual benefit in improving respiratory dynamics as well as pain control. Not all interventional techniques are feasible as an inpatient, so close follow-up must be arranged for discharge.

The intubated and mechanically ventilated patient poses additional challenges in not only pain assessment but also in pain management. The higher incidence of multi-organ failure leads to opioid medications having an increased incidence of side effects. As was previously discussed in this chapter, the opioid selected provides dual effect as a sedative and analgesic but can delay ventilator weaning in kidney or hepatic failure if an active metabolite accumulates. Multiple modalities can still be utilized in these patient populations since drugs such as NSAIDs, gabapentin, and acetaminophen come in a variety of formulations.

The aforementioned pain assessment tools must be employed at regular intervals to ensure appropriate and ongoing evaluation of a patient's pain level. This ensures that patients who require an escalation in care due to inadequate pain control or de-escalation secondary to adverse effects are identified. Complementary approaches to pain management can also be incorporated where the services exist as inpatients. Physical therapy, cognitive behavioral therapy (CBT), acupuncture, transcutaneous electrical nerve stimulation, and yoga have shown benefit as components of multimodal approaches; however, not all these modalities may be available in all institutions [53, 86]. No two patients are alike, so clinicians must remain flexible and vigilant in their pain management plans, as multiple medications or therapies may be trialed before a beneficial response is achieved.

12.8 Discharge Plan for Pain Management

When patients are discharged from the hospital, follow-up should be arranged with sufficient medication prescriptions provided to bridge patients to future appointments. The benefit of multimodal therapy extends beyond a hospital admission. Continue all non-opioid adjuvants, especially when opioid medications are being prescribed. Patients who were discharged on opioids alone were more likely to have readmissions and higher pain scores on follow-up within 30 days when compared with patients who received adjuvant medications with opioids [90]. When discharged on a multimodal analgesic regimen, patients required 10–40% less opioids daily [90].

Patient education is critical as patients who are discharged with pain often have clinically significant pain within a week but lack an understanding of what can be done to alleviate the pain or how to appropriately utilize prescribed therapies [91]. Clearly written instructions with thorough explanations to the patient and family or caregivers is essential upon discharge. Education should also include the potential long-term risks of prescribed medications with both appropriate and inappropriate use as well as alternative considerations if pain persists. Arranging follow-up with the patient's primary care clinician or pain management specialist should depend on the patient's needs. Referral to a pain clinic should not be delayed if necessary. Ideally referral should be made within 4–6 months of chronic pain appearing to prevent the long-term disability that can emerge when psychological, environmental and behavioral contributors to pain persist [92]. Alternatively, patients who benefitted from an interventional procedure such as a PVB may require additional blocks in an outpatient setting so close follow-up should be arranged with an interventional pain management specialist.

As an outpatient, continuation of complementary therapies such as pulmonary rehabilitation should be organized for the patient. Encourage follow-up with a physical rehabilitation center to improve mobility and posture. Alternative therapies such as acupuncture and massage have been shown to be effective for neck and shoulder pain, which is commonly present in pulmonary conditions [93, 94]. Patients that still meet the criteria for arterial hypoxemia need home oxygen therapy arranged. The Stepped Care for Affective Disorders and Musculoskeletal Pain (SCAMP) trial showed patients with co-morbid depression and musculoskeletal pain may benefit from venlafaxine or a serotonin selective reuptake inhibitor such as sertraline with a pain self-management plan emphasizing behavioral changes and social supports [95]. Referral to psychologists may be warranted in patients with poor coping skills or feelings of hopelessness, as CBT has shown modest benefit in chronic pain [53]. Ensuring patients are well informed and have sufficient follow-up are essential components to discharge and preventing the long-term adverse effects of inadequately managed pain in patients with pulmonary disease.

12.9 Summary

- Initial work-up of patients requires an in-depth history and physical examination
- Non-cardiac chest pain requires thorough cardiac work-up as part of acute evaluation
- Imaging studies are useful in guiding diagnoses of respiratory illness
- Treatment of underlying condition can alleviate some of the associated pain, particularly with pleuritic type chest pain
- The pain assessment tool used should be validated in a specific population and is an important factor in determining response to pain management interventions

- An individualized pain management plan should be communicated with both the patient and the primary medical or surgical team
- The pain assessment tool used should be validated in a specific population
- Disadvantages and advantages of interventions need to be considered prior to initiation as well as explained to the patient with reasonable alternatives
- Medication therapy should be tailored for each patient and should follow a stepwise approach, maximizing the use of non-opioid adjuvant medications. Opioids may be added if pain remains poorly controlled, but close monitoring must be utilized
- Interventional techniques should be reserved for patients who have pain refractory to more conservative approaches
- Arrange outpatient follow-up for patients with chronic pain secondary to respiratory conditions and for further interventional approaches

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Chapter 13
Inpatient Pain Management in Patient with Opioid Use Disorder

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13.1 Introduction

Physicians across all disciplines interface with patients with opioid misuse in the setting of the current opioid epidemic. More than two million individuals meet criteria for an OUD and ten million people misuse opioids [1]. Pain physicians will encounter these patients as inpatients, in the emergency room, or in the preoperative area. Pain physicians need management strategies to best care for this high-risk patient population.

Pain management is notably more complex in patients with opioid misuse and OUD. These patients may be on prescription opioids, illicit substances, or one of three FDA-approved medications for OUD (methadone, buprenorphine, or extended-release injectable naltrexone). Opioid-tolerant patients present particular challenges with more complex neurobiological alterations including opioid dependence, opioid misuse, opioid-induced hyperalgesia, withdrawal, and comorbid substance use and psychiatric disorders [2, 3]. Pain assessments are complicated and the clinician must differentiate between appropriate pain relief and potential drug-seeking behaviors. Acute pain management in these patients is best managed by a multimodal approach using non-opioid medications such as ketamine, lidocaine infusions, dexmedetomidine and regional anesthetic techniques.

The majority of individuals with OUD are not receiving treatment with MOUD which includes opioid agonist (buprenorphine or methadone) or opioid antagonist therapies (extended-release injectable naltrexone) [1]. The inpatient setting may be

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an ideal time to transition these patients onto one of these treatments. The choice of treatment should be a shared decision between the clinician and patient. Discharge planning and coordinating follow up is vital to preventing risk of relapse after discharge from the hospital.

This chapter will review best pain management strategies for patients with opioid misuse and OUD, how to initiate MOUD, and discharge planning with careful consideration of psychiatric comorbidity and risk for relapse in this high-risk patient population.

13.2 Historical Perspective

The rise and more liberal use of opioids for pain in the 1990s was related to a confluence of factors including the observed safety and effectiveness profile, the aggressive promotion of opioids, several new opioid formulations including OxyContin in 1995, and endorsements by national organizations. The American Academy of Pain Medicine (AAPM) and the American Pain Society (APS) adopted a consensus statement encouraging use of opioids for chronic pain stating that "studies indicate that de novo development of addiction when opioids are used for relief of pain is low" [4]. The Joint Commission recommended that pain be regularly evaluated as the "fifth vital sign" in hospitalized patients [5]. This historical shift toward liberality in opioid prescriptions resulted in unintended consequences and contributed to the rise in opioid overdose deaths [6, 7].

13.3 Opioid Pharmacology and Neurobiology

The rewarding and analgesic effects of opioids are predominantly mediated through agonist effects at the μ-opioid receptor and engaging the endogenous opioid system [8]. Brain regions that regulate pain perception (periaqueductal gray, thalamic cortex, and insula) and pain emotional responses (amygdala) contain high μ-opioid receptor levels. These receptors are highly concentrated in brain regions associated with the reward networks (ventral tegmental area, nucleus accumbens) and opioids can be perceived as highly pleasurable or rewarding contributing to addiction [9]. The brainstem respiratory center (pre-Bötzinger complex) is also highly concentrated with μ-opioid receptor levels and depresses respiration and can result in opioid overdose-induced death [10]. Opioid medications vary in their binding affinity and selectivity for the mu, kappa, and delta opioid receptors with variable potency. The different pharmacokinetics and bioavailability influence reward and addiction potentials. Diverted opioids are snorted or inject for more rapid and direct stimulation of brain reward centers. Abuse-deterrent opioid formulations are encouraged by the

FDA and designed to prevent opioids being snorted or injected [11, 12]. For instance, the naloxone component in Suboxone (buprenorphine and naloxone) is present to deter injection.

13.4 Physical Dependence

Physical dependence is distinct from addiction. All patients receiving opioids for pain or misusing opioids will develop physical dependence. This refers to the emergence of withdrawal symptoms when opioids are abruptly discontinued, or tapered, after long-term administration. Withdrawal symptoms include piloerection, insomnia, cramps, diarrhea, nausea, vomiting, body aches, dysphoria, anxiety, and irritability [3]. The severity of these symptoms varies depending on chronicity and opioid medication potency [13]. Dependence can lead to opioid seeking in individuals avoiding withdrawal symptoms. This can lead to opioid misuse and with repeated exposures increases susceptibility to addiction.

13.5 Opioid Misuse

Opioids can be misused for avoidance of withdrawal symptoms, analgesic effects, and for rewarding properties. Misuse refers to using opioid prescription other than as prescribed. Individuals seeking rewarding effects might snort or inject to have rapid brain stimulation of reward centers [14]. Oral misuse involves higher opioid requirements and might be combined with other substances. Opioid misuse does not directly result in addiction, although as in the setting of physical dependence, repeated exposures increases risk of developing addiction. Prescribing clinicians can access Prescription Drug-Monitoring Programs (PDMPs) to see prescriptions, patterns of use, and if accessing from other providers (although individuals may be using illicit substances or obtaining opioids from friend or relative).

13.6 Hyperalgesia

Heightened pain sensitivity (hyperalgesia) can occur in susceptible individuals with repeated exposure to opioid analgesics. Dose tapering or opioid discontinuation can result in improvement in pain. It is challenging for clinicians to decide when to increase or decrease opioid analgesics in this setting and there is limited evidence of clinical strategies to prevent hyperalgesia [15].

13.7 Addiction

Addiction or a substance use disorder is different from physical dependence and develops more gradually. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) characterizes a substance use disorder by a pronounced craving and preoccupation for the substance, inability to refrain from using it, and escalation of use despite negative consequences [16]. The development of a substance use disorder involves neurobiological processes including learning mechanisms that consolidate automatic behaviors in response to a substance and associated stimuli. The pleasurable effects of opioids and many other addictive substances are related to dopamine release in the nucleus accumbens, the key reward region [17]. This results in conditioning where there is a learned association between administration of the substance and pleasure. Conditioning to opioids can occur from rewarding effects, from pain relief, withdrawal symptoms, or dysphoria. With repeated exposures, conditioning is strengthened and fuels the desire and motivation to consume the substance [18]. These repeated exposures disrupt the neurocircuitry in the basal ganglia, prefrontal cortex, and extended amygdala. The disruption to the extended amygdala which regulates emotions and stress leaves the individual susceptible to dysphoria, depression, anxiety, and irritability [19]. Changes in the striatocortical circuits which are necessary for proper functioning of the prefrontal cortex and important in self-regulation can present as impulsivity and other dysregulated behaviors in individuals. These neurocircuitry changes are mutually reinforcing and contribute to the relapsing nature of substance use disorders. Even following substance discontinuation, these changes can persist which is why continuous and comprehensive care is needed for recovery.

13.8 Risk Factors

OUD is etiologically complex and is difficult to predict in advance of an initial opioid prescription [20]. Risk factors to developing OUD include history of other substance use disorders, comorbid psychiatric disorders, suicidal history, prior overdose, long-term opioid therapy and higher daily dosing seen in Table 13.1 [21–32]. Nearly one-third of patients on chronic opioid therapy develop addiction, although there is little knowledge regarding the risk of short-term (less than 2 weeks) of opioid therapy following an emergency room visit or acute injury [26]. Individuals on opioid doses greater than 90-mg morphine equivalents daily and longer-acting opioids, such as methadone and oxycodone, are at increased risk of overdose. Concomitant use of alcohol and sedatives such as benzodiazepines and baseline respiratory disease also increase risk of overdose [21, 27]. Prior suicide attempts and intentional/unintentional overdoses are associated greater risk of overdose [22, 26]. A thorough initial evaluation and history is important for identifying these risk factors and considering psychiatric consultation for further management. Various risk factors for opioid overdose and developing OUD are listed in Table 13.1.

Table 13.1 Factors associated with risk of opioid overdose and OUD [21–23]

Factor	Risk
Medication-related	
Daily dose >90 MME	Overdose, OUD
Long-term opioid use (>3 months)	Overdose, OUD
Coadministration of benzodiazepines	Overdose
Long-acting or extended-release formulation (methadone, oxycodone, fentanyl patch)	Overdose
Period shortly after initiation of long-acting or extended-release formulation (<2 weeks)	Overdose
Patient-related	
Age > 65 years old	Overdose
Adolescence	OUD
Respiratory disease	Overdose
Renal or hepatic impairment	Overdose
Psychiatric disorder (depression, anxiety disorder, personality disorders)	Overdose, OUD
Substance use disorder	Overdose, OUD
History of overdose	Overdose
History of suicidality	Overdose

13.9 Psychiatric Considerations for the Inpatient

13.9.1 Psychiatric and Substance Use Disorders Comorbidity

Individuals with OUD and opioid misuse are more likely to have co-occurring psychiatric disorders including depression, anxiety, PTSD, personality disorders, and other substance use disorders (tobacco, alcohol, benzodiazepines, stimulants, and cannabis) [1, 2]. This is bidirectional where those with any mental illness are three times as likely to have concurrent opioid misuse with opioid prescriptions and develop OUD. The majority of those misusing opioids reported misuse for pain relief. According to the 2018 National Survey on Drug Use and Health (NSDUH), an estimated nine million adults in the United States had a substance use disorder and co-occurring mental illness. Amongst this population, about half received treatment for co-occurring mental illness and substance use disorder [1].

Paralleling the opioid epidemic is an overall increase in completed suicides, linked to opioid overdose deaths. Individuals with OUD have a suicide risk of 87 per 100,000 people, 16 times greater than that of the general population rate (14 per 100,000). It is estimated that nearly 30% of opioid overdose deaths represent a suicide and this percentage may in fact be higher [23].

Psychiatric symptoms and assessment can be complicated in the setting of substance use where individuals might experience dysphoria, anxiety, difficulty sleeping, suicidality, and irritability in withdrawal states, or even in the context of substance intoxication on initial presentation [2]. Comprehensive psychiatric assessment is needed to further assess for primary psychiatric disorders in acute inpatient settings

and appropriately assess risk. Psychiatric specialists are key in addressing psychiatric comorbidities and offering interventions while inpatient. Psychopharmacological management and psychosocial interventions (cognitive behavioral therapy, motivational interviewing, contingency management) can be initiated while inpatient and patients can be linked to outpatient services [28].

13.9.2 Identifying Risk Factors and Screening

Pain management providers commonly encounter patients with opioid misuse and OUD. Many of these individuals are not receiving treatment, and are at high risk for poor outcomes [1]. Acute inpatient settings provide an opportunity to identify those at risk, refer to treatment, and tailor pain management regimens appropriately. A thorough initial evaluation and history is important for identifying risk factors noted in Table 13.1. Obtaining an accurate history can be challenging as patients may not be as forthcoming due to previous negative experiences, stigma, and fear that pain will be undertreated or the OAT dose will change considerably or be discontinued [29]. With the patient's consent, it is recommended to speak to a significant other or family member who can corroborate psychiatric and substance use history.

Evidence-based screening tools for substance use should be part of the initial assessment. The Substance Abuse and Mental Health Services Administration (SAMHSA) site has multiple tools accessible to clinicians [30]. The Opioid Risk Tool in Fig. 13.1 can be used to screen for opioid misuse on the initial encounter or in patients being prescribed opioids. A score 3 or lower indicates lower risk for opioid misuse, 4–7 moderate risk, and 8 or greater indicates high risk for opioid misuse [31]. The CAGE-AID in Fig. 13.2 is a brief four-question screening tool for substance use. A positive response to one or more questions is considered a positive screen [32]. Another routine screening that can be used in the acute care setting is SBIRT or Screening, Brief Intervention, and Referral to Treatment seen in Fig. 13.3 [33]. Although SBIRT helps to identify patients with OUD, it has not demonstrated any impact on meaningful reductions in opioid use on its own likely related to few patients with adequate follow-up or referrals. It is suggestive that patients may benefit from more immediate intervention prior to discharge with buprenorphine induction and better linkage to outpatient care [34]. If a patient screens positive then the treatment team should involve psychiatric and addiction specialists in the patient's care while in the inpatient setting with appropriate outpatient referrals or communication with outpatient providers upon discharge.

13.9.3 Relapse Prevention and Pain Assessment

The primary focus of the pain management provider in the inpatient setting should be to provide adequate analgesia while minimizing the risk of relapse. Individuals with OUD are more likely to relapse when pain is undertreated in the inpatient

Opioid Risk Tool

Mark Each Box That Applies	**Female**	**Male**
1. Family history of substance use		
Alcohol	☐ 1	☐ 3
Illegal drugs	☐ 2	☐ 3
Prescription drugs	☐ 4	☐ 4
2. Personal history of substance use		
Alcohol	☐ 3	☐ 3
Illegal Drugs	☐ 4	☐ 4
Prescription drugs	☐ 5	☐ 5
3. Age between 16-45 years	☐ 1	☐ 1
4. History of pre-adolescent sexual trauma	☐ 3	☐ 0
5. Psychological disease		
ADHD, OCD, bipolar disorder, schizophrenia	☐ 2	☐ 2
Depression	☐ 1	☐ 1
Scoring Totals	_____	_____

Fig. 13.1 Screening tool for opioid misuse [32]

CAGE-AID Questions	**Yes**	**No**
1. Have you ever felt that you ought to **C**ut down on your drinking or drug use?	☐	☐
2. Have people **A**nnoyed you by criticizing your drinking or drug use?	☐	☐
3. Have you ever felt bad or **G**uilty about your drinking or drug use?	☐	☐
4. Have you ever had a drink or used drugs first thing in the morning (**E**ye-opener) to steady your nerves or to get rid of a hangover?	☐	☐

Fig. 13.2 Screening tool for substance use [33]

setting [28, 35]. Opioid analgesic requirements are often higher due to increased pain sensitivity and opioid cross-tolerance. Additionally, states of acute withdrawal can further heighten pain sensitivity [28, 36]. Patients at high risk for opioid overdose and with OUD need appropriate outpatient treatment referrals or communication with current providers prior to discharge. Individuals with OUD

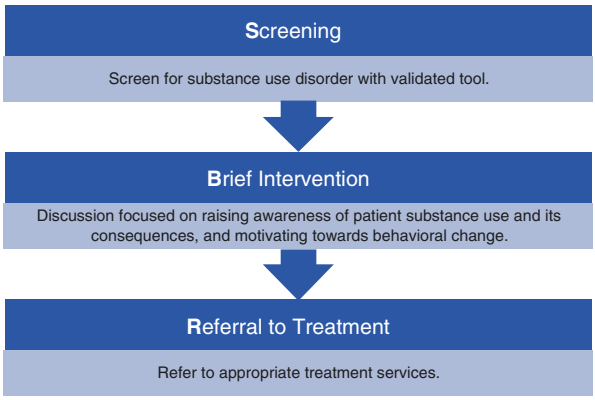

Fig. 13.3 Screening, Brief Intervention, and Referral to Treatment (SBIRT) [17]

not on opioid agonist treatment following detoxification have a relapse rate greater than 90% and higher rates of HIV, HCV, homelessness, and death [2, 37]. Individuals meeting diagnostic criteria for OUD should be recommended MOUD (buprenorphine, methadone, or extended release injectable naltrexone) when feasible to start in the inpatient setting. If unable to start while inpatient, individuals should be connected with outpatient substance use treatment to reduce risk of relapse and overdose.

According to the International Association for the Study of Pain, pain is defined as "unpleasant sensory and emotional experience associated with actual or potential tissue damage" [38]. Currently the gold standard for pain assessment is subjective assessments though self-assessments. Clinicians must correlate perceived pain with that expected based on diagnostic workup and clinical findings. Currently there is not a validated assessment tool to distinguish subjective pain from drug-seeking presentations.

13.10 Inpatient Management of Patients on Opioids

13.10.1 Prescription Opioids

Common opioids prescribed in the outpatient setting include oxycodone, hydromorphone, morphine, and hydrocodone. Managing a chronic opioid user's acute pain starts with a detailed history of their chronic daily opioid requirements. It is always best to verify medications and doses with the prescribing physician, distributing pharmacy, and state Prescription Drug-Monitoring Programs (PDMPs). This information will be used to calculate the patient's total daily dose (TDD) in oral morphine equivalents (OME). Table 13.2 lists equianalgesic doses of commonly used opioids.

In the setting of acute pain, the outpatient basal TDD will typically need to be increased by 25–50%, which will be called the adjusted TDD (aTDD) [39]. The aTDD should be prescribed to the patient in the form of a long-acting opioid that will provide a basal level of analgesia and prevent withdrawal. This is commonly

Table 13.2 Equianalgesic dosages of commonly used opioids [39, 40]

Opioid	Oral dose (mg)	Intravenous dose (mg)
Morphine	30	10
Tramadol	150	n/a
Codeine	200	n/a
Hydromorphone	7.5	1.5
Oxycodone	20	n/a
Hydrocodone	30	n/a
Oxymorphone	10	n/a
Fentanyl	n/a	0.1

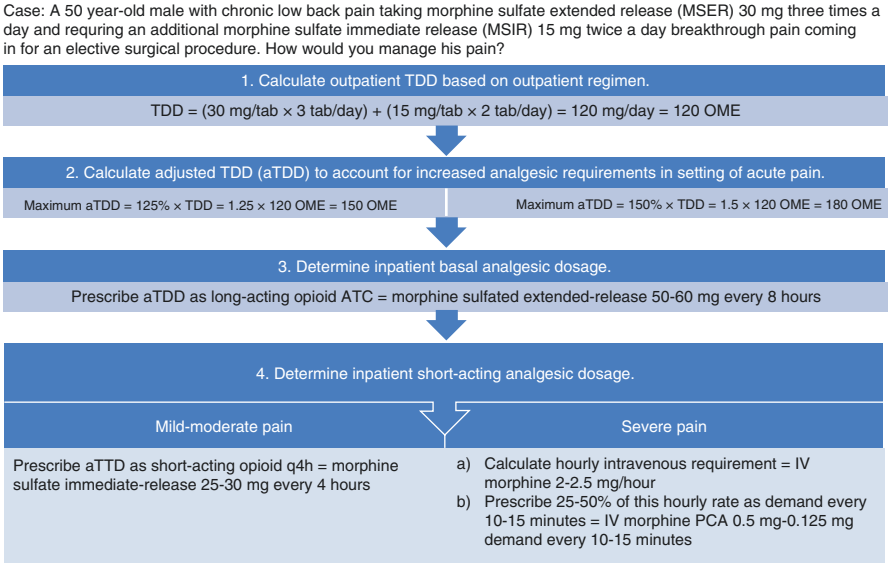

Fig. 13.4 Sample case of opioid dosing in chronic opioid user in patient with acute on chronic pain

done with extended-release oxycodone or extended-release morphine. Intravenous medications can be used for patients not tolerating oral medications.

Patients will need additional short-acting opioids for controlling acute pain. Oral opioids are usually adequate for mild-moderate pain. In this scenario, the aTDD should be prescribed as a PRN in the form of short-acting medications every 3–4 h on top of the basal dosing. For severe pain, patient-controlled analgesia is a more appropriate option as it allows more rapid titration of analgesics and effective control of pain with reduced risks of side effects. In these cases, the aTDD should be converted to total hourly intravenous opioid requirements. About 25–50% of this hourly dose should be given as PCA demand every 10–15 min. The inpatient goal should be to transition patients to oral opioids as soon as possible. Patients should then be weaned off back to their chronic opioid regimen as soon as the acute pain episode has resolved. This will require close communication with the patient's outpatient provider and setting expectations with the patient. A sample case is demonstrated in Fig. 13.4.

13.10.2 Special Scenarios

13.10.2.1 Intrathecal Opioids

Intrathecal opioid infusion should be continued to maintain baseline opioid requirements. However, certain circumstances may prevent the continuation of the intrathecal opioid infusion such as pump malfunctions or for surgical needs. In this case, an equianalgesic intravenous infusion should be started [40]. Although morphine is the only opioid with FDA approval for intrathecal use, fentanyl and hydromorphone are also often used off-label. The accepted guidelines for conversion of hydrophilic opioids such as morphine and hydromorphone from intrathecal to intravenous is 1:100. The accepted conversion ratios for fentanyl are not well established. Based on expert opinion, case series, and one retrospective chart review the ratio for intrathecal to intravenous fentanyl ranges between 1:20–100 [41]. A table with intrathecal and intravenous opioid conversions is shown in Table 13.3. The conversion ratios between two intrathecal opioids is complex and beyond the scope of this chapter.

13.10.2.2 Transdermal Patches

Transdermal opioid patches, commonly fentanyl, should typically be removed preoperatively. Fentanyl patches work by releasing a designated amount of fentanyl across the skin barrier. An intracutaneous reservoir starts developing from initial application of the patch, typically reaching steady-state over 24–72 h [42]. Fentanyl is then absorbed into the systemic circulation from this intracutaneous reservoir through cutaneous vasculature [43]. Even after removal of a patch, it takes about 17 h for serum fentanyl concentration to decrease by 50% due to the size of the reservoir [42].

Perioperative changes can alter absorption at two different stages along this pathway. First, and most widely recognized, is the direct application of warming devices that can cause the patch to release excessive amounts of fentanyl. This can be avoided by removal of the device. However, patients will continue to have significant intracutaneous reservoirs several hours after removal of the patch. Both anesthetic agents and peripheral warming devices will cause cutaneous vasodilation, which can also cause excessive systemic absorption [42, 43]. Case reports have described opioid overdoses from transcutaneous patches even after removal [44].

Table 13.3 Conversion factors between intrathecal and intravenous dosages for various opioids [41]

Opioid	Intrathecal: intravenous ratio
Morphine	1:100
Dilaudid	1:100
Fentanyl	1:20–100

13.10.3 Illicit Drugs

13.10.3.1 Controlled Prescription Opioids

Controlled prescription drugs (CPD) are the second-most commonly used illicit drugs in the United States (after marijuana) and are responsible for the most drug-involved overdose deaths. Sixty-two percent of these users report using them for relief of physical pain and only 13% report using them for euphoric purposes. Fifty-three percent of CPDs are obtained from close friends or relatives. Thirty-seven percent are obtained directly from physician prescriptions. Although these CPDs are illicitly obtained, one should be able to calculate daily opioid requirements when these patients are admitted to the inpatient setting. However, it is important to note that increasing numbers of counterfeit prescription pills are distributed containing mixtures of other opioids and drugs, making it difficult to assess the true dosages that the patient is consuming [45].

13.10.3.2 Heroin and Synthetic Opioids

Heroin and synthetic opioids, like fentanyl, are the two other types of illicit opioids that are commonly used for abuse in the United States. To the best of our knowledge, there is no literature supported equianalgesic conversion of these drugs to OME. The purity of these drugs is largely variable and they are often mixed with other substances [45]. Thus, it is best to start with conservative estimates of opioid requirements and be prepared to aggressively titrate the dosing according to response.

13.11 Inpatient Management of Patients on OUD Pharmacologic Treatment

13.11.1 Methadone

13.11.1.1 Pharmacology

Methadone was first used to treat OUD in the 1950s [40] and received FDA approval in 1972 [46]. Since then, it has been used for intraoperative and postoperative analgesia in spine and cardiac surgeries [47]. Methadone is a synthetic mu-opioid of the diphenylpropylamine class that is formulated as a racemic mixture. Levomethadone, the R-enantiomer, provides the direct opioid effect [47, 48]. Dextromethadone, the S-enantiomer, acts as an NMDA-antagonist, serotonin reuptake inhibitor [47], and a norephinephrine reuptake inhibitor. It is theorized that the methadone's effect on preventing opioid-induced hyperalgesia and effectiveness on neuropathic pain is driven by the actions of dextromethadone [47].

Methadone undergoes hepatic metabolism via the CYP3A4, CYP2B6, and CYP2C19 into inactive metabolites. It is then primarily renally excreted with some contribution from the fecal route [47, 48]. Because of genetic variability in the function of these particular enzymes, methadone has widely variable half-life [47]. Methadone undergoes a biphasic elimination with initial alpha-elimination half-life of 8–12 h and beta-elimination half-life of 30–60 h. The former explains methadone's analgesic duration of action and the latter explains the duration of its withdrawal suppression [47].

Compared to other opioids, one of the unique side effects of methadone is QT prolongation, which is mediated through dextromethadone's effect on the human ether-a-go-go receptor. Most cases of Torsades de Pontes have occurred in patients on large, chronic doses typically greater than 200 mg/day. A general best practice is to consider a baseline EKG prior to initiation or after changing dosage in high-risk patients, such as the elderly, females, patients with history of hepatic dysfunction, prior cardiac history, or baseline QT prolongation [47].

13.11.1.2 Perioperative Management

Methadone should be continued perioperatively as it will provide a basal opioid level to prevent withdrawal and craving without impeding the ability to provide analgesia as it is a full mu-agonist [46]. Typical maintenance dosing ranges from 60 to 120 mg/day. One consideration is to adjust the dosing from daily to every 6–8 h [40, 46]. Such an adjustment will allow for a more stable serum concentration that remains within the analgesic window for a larger percent of time [40, 46, 48]. In the outpatient setting, daily dosing is appropriate in the outpatient setting when the goal is to prevent withdrawal. In patients who are unable to tolerate oral medications, the oral to parenteral conversion is on average 2:1, but providers need to be aware of the widely ranging oral bioavailability from 36 to 100% [47].

Additional medications will be needed to control acute pain. Multimodal analgesia must be implemented, as these patients are tolerant to opioids and intolerant to pain [48]. Further details will be provided later in this chapter. An opioid PCA may be necessary for patients with moderate to severe pain.

13.11.2 Buprenorphine

13.11.2.1 Pharmacology

Buprenorphine was first introduced into clinical practice in the late 1970s. It received FDA approval for treatment of acute pain in 1981 as a parenteral medication. However, it wasn't until 2002 that it was approved for treatment of OUD in the sublingual form. More recently, it has been approved as a weekly or monthly injection [48], or biannual subdermal implant [46].

Buprenorphine is a partial mu-receptor agonist and full kappa-receptor antagonist with high affinity relative to other opioids. With a typical buprenorphine dose, >80% of mu receptors will be occupied with just 40% potency of a full agonist [46], providing it with its unique ceiling effect properties [40]. This prevents euphoric effects patients can achieve [46] while also preventing withdrawal. However, because of this property, extra caution must be taken when starting a patient on buprenorphine. It is usually started with doses 2–8 mg/day and increased weekly [40]. Therapeutic doses range between 8 and 24 mg/day [46], but may be as high as 32 mg/day [40]. Although sublingual buprenorphine is typically dosed daily, its effect will continue to occupy mu receptors with decreasing affinity for up to 4 days after discontinuation [40]. It has CYP450 3A4 metabolism and biliary excretion [48]. One limitation to the use of buprenorphine is that it must be started when the patient is in a state of withdrawal. This will be discussed in more detail later in this chapter.

Buprenorphine is often prepared in a 4:1 ratio with naloxone to prevent abuse. If injected parenterally, naloxone prevents the euphoric effects that patients may achieve from buprenorphine. Naloxone has very low bioavailability with sublingual ingestion due to first pass metabolism and thus has little effect when the medication is administered as indicated [48].

13.11.2.2 Perioperative

At this time, there is no consensus recommendation on management of buprenorphine in the setting of acute pain, including surgery [40, 46, 48]. Given buprenorphine's high affinity and only partial agonism, the general concern in the medical community is that buprenorphine could limit analgesic efficacy of other opioids [48]. Based on this theory, providers would typically hold a patient's buprenorphine for up to 5 days prior to an elective procedure to facilitate optimal analgesia. However, more recent data suggests that adequate analgesia can be achieved despite continuation of buprenorphine and is now increasingly becoming the accepted perioperative strategy.

The spectrum of options ranges from full cessation 5 days prior to surgery to continuation of buprenorphine throughout the perioperative period. The two primary factors that need to be considered are risk of relapse and ability to provide adequate analgesia. An algorithm for the management of perioperative buprenorphine is shown in Fig. 13.5.

Discontinuation 5 Days Prior

With this approach, the patient will need to be transitioned to some other opioid to control withdrawal and craving symptoms. This can either be short-acting opioids such as oxycodone or long-acting such as methadone [40]. Stopping buprenorphine places the patient at risk of relapse, especially with short-acting medications which

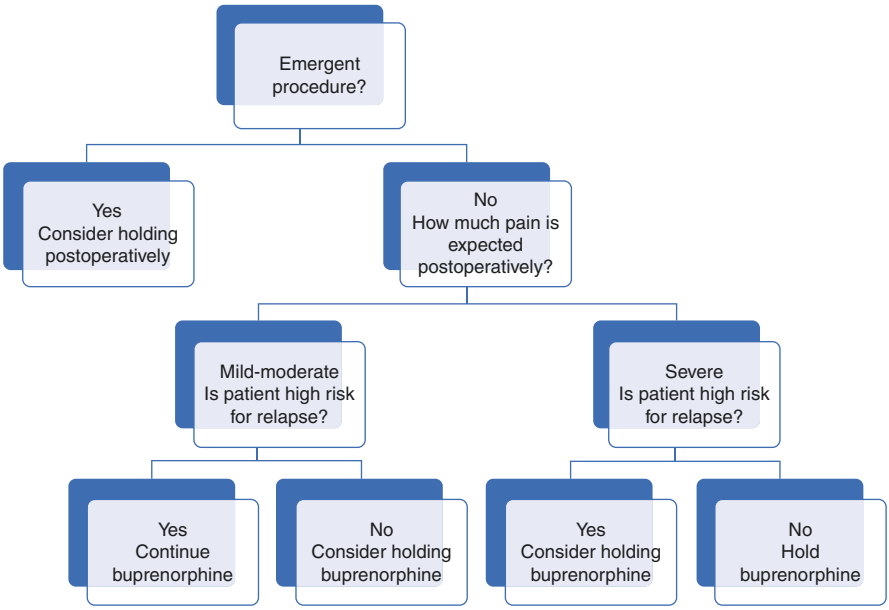

Fig. 13.5 Algorithm for the management of perioperative buprenorphine perioperatively

can cause periods of euphoria and craving. According to data from 2015, 80% of patients with OUD started with prescription opioids [40]. If converting the patient to methadone, the typical conversion from buprenorphine to methadone is 1:5 [40]. For example, a patient on 16 mg of oral buprenorphine should be started on 80 mg of oral methadone. Transitioning the patient back after surgery exposes the patient to risks associated with undergoing another buprenorphine induction.

Perioperative Continuation

This strategy will allow patients to continue their OUD treatment uninterrupted. Even with high buprenorphine doses, there will still be some unoccupied mu receptors that can be targeted with opioids. In addition, buprenorphine will provide some analgesic effect as that was its original indication when introduced into clinical practice in the 1980s [48]. With the increasing emphasis and knowledge on multimodal analgesia, there is increasing evidence to suggest that perioperative pain can be adequately controlled despite continuation of buprenorphine [46]. Strategies for multimodal analgesia will be discussed later in this chapter. Despite this, the inpatient provider should be prepared to use higher dose opioids with aggressive titration to overcome the buprenorphine blockade, ideally with other high-affinity opioids such as sufentanil and fentanyl.

There is no consensus approach and the strategy must be individualized to each patient. The stress of surgery, uncontrolled pain, and the fear of uncontrolled pain can all trigger relapse. At the same time, access to short-acting opioids and undergoing

repeat buprenorphine induction can also do the same. The ideal approach for any patient thus needs to be made with careful discussion with the outpatient provider, patient, and the inpatient provider to determine what is best for the patient.

13.11.2.3 Special Scenarios

Injectable/Depot Formulations

These formulations are great options in patients who are unable to reliably take their medications daily. However, because of their duration of action, holding these medications in advance of procedures is impractical without exposing the patient to significant risk of relapse. Elective procedures should be scheduled just prior to the subsequent dosing if possible.

Emergent Surgery or Pain

In these situations, the inpatient provider will need to implement multimodal analgesia as well as using higher dose opioids than usual to adequately control the acute pain. The inpatient provider will need to decide on whether subsequent doses of buprenorphine should be held to facilitate analgesic needs. This decision should ideally be made with the input from both the patient and the outpatient provider.

If the buprenorphine is held, the patient will need to be closely monitored for signs of respiratory depression. As the remaining buprenorphine is excreted from the circulatory system, the patient will be increasingly susceptible to the effects of the full opioid agonist due to a loss of competitive inhibition for the mu receptors. Patient controlled analgesia are an ideal option to minimize risk of such complications.

Pregnancy

The American Society of Addiction Medicine recommends continuation of buprenorphine before elective cesarean deliveries to avoid risk of fetal opioid withdrawal [46].

13.11.3 Naltrexone

13.11.3.1 Pharmacology

Naltrexone is a semi-synthetic opioid antagonist used in the treatment of alcohol-dependence and opioid-dependence [40]. Naltrexone is available as a daily-dosed oral formulation and a monthly-dosed injectable formulation. Half-life of the oral formulation is about 10 h in patients with continuous use [48].

Patients on naltrexone need to be monitored closely when being administered opioids. While mu receptors are occupied by naltrexone, other opioids will have little analgesic effects [46]. However, during this time, the mu receptors are upregulated due to the lack of stimulation. Thus, once naltrexone is no longer occupying the receptors, patient will have increased sensitivity to opioids.

13.11.3.2 Perioperative Management

Elective Cases

There is a consensus among the medical community that naltrexone should be held prior to elective procedures [40, 46, 48]. With the oral formulations, it is recommended to hold the medication for 72 h prior to surgery. With the injectable formulation, cases should be scheduled at least 4 weeks after the previous injection.

Time-Sensitive Procedures

For emergent and urgent procedures, naltrexone dosing should be held as soon as possible. An analgesic plan with a heavy emphasis on non-opioid analgesia should be developed [40, 46, 48]. In some animal studies 6–20 times greater doses of opioids were needed to achieve analgesia during full mu antagonism. These patients will need to remain in a monitored setting due to their rapidly changing sensitivity to opioids.

The peak effect of the injectable formulation occurs after 1 week. Opioid based analgesia will have minimal effect during the first 2 weeks after injection. If a case cannot be delayed 28 days, one can consider scheduling it during the fourth week after injection [48].

Of the three OUD-controlling medications, naltrexone is the highest risk for causing withdrawal with induction. The FDA-approved prescribing information advises patients to be abstinent from opioids for 7–10 days prior to induction, which is especially difficult after a surgical procedure. The inpatient provider needs to communicate with the outpatient provider to develop a plan for re-induction back onto naltrexone.

13.11.4 Multimodal Analgesia

13.11.4.1 Ketamine

Ketamine is a phencyclidine analog that was first used to as a general anesthetic in the 1960s. It is known for its dissociative anesthesia associated with psychomimetic side effects. However, recently, it has also been used for treatment of chronic pain via its hypothesized ability to reverse the effects of central sensitization and for

severe depression. More recently, ketamine has also drawn interest as a component of multimodal analgesia [49].

Ketamine exudes its anesthetic properties through its antagonism at the NMDA receptor and agonism at mu-receptors. Thus far there have only been four randomized-control trials examining the benefits of perioperative ketamine in patients with opioid-dependence. The largest of these trials by Loftus et al. enrolled 102 patients undergoing spine surgery. The findings revealed a reduction in opioid consumption at 48-h and 6-weeks postoperative. The other three studies had equivocal results but may have been limited due to being underpowered and using smaller ketamine doses [50]. The largest of the three studies had a sample size of 60 patients; and maximum doses used were a 0.2 mg/kg bolus and an infusion of 0.2 mg/kg/h [49].

Based on this data, the American Society of Regional Anesthesia and Pain Medicine (ASRA) recently published guidelines recommending perioperative ketamine use in this population. The benefit of ketamine is likely to be greater in patients undergoing surgeries with severe postoperative pain, such as abdominal, thoracic, and orthopedic procedures, and in patients at higher risk of opioid-related side effects such as obstructive sleep apnea. Data behind use in non-surgical acute pain exacerbations is limited to case series and reports. However, it has been used successfully as an analgesic in many pathologies ranging from sickle cell disease to renal colic to pancreatitis [49].

A majority of acute pain studies have used boluses less than 0.5 mg/kg and infusions at less than 0.5 mg/kg/h. The Loftus study focusing on opioid dependent patients used an initial bolus of 0.5 mg/kg followed by an infusion at 0.6 mg/kg/h. However, based on an analysis of all of these studies ASRA has recommended that initial boluses remain less than 0.35 mg/kg followed by an infusion less than 1 mg/kg/h. Higher doses may be given on case-by-case basis, but will likely require ICU monitoring. In addition, regardless of these guidelines, providers need to always be cognizant of side effects including risk of aspiration, cardiovascular side effects, and psychomimetic side effects. Risk of these side effects can be mitigated by addition of ketamine with an opioid-based PCA. Typical demand doses of ketamine have ranged from 1 to 5 mg/bolus. Although PCA administration is not yet as common as infusions, it demonstrated a reduction in pain, opioid requirements, and decreased PONV without an increased in psychomimetic side effects. Relative contraindications to ketamine use include poorly controlled cardiovascular disease, active psychosis, pregnancy, cirrhosis, elevated intracranial pressure, and elevated intraocular pressure.

There is current ongoing research looking into potential oral and intranasal formulations for ketamine. These are both currently off-label uses of the drug, but have been used in a handful of studies. Preliminary studies suggest intranasal ketamine may be an ideal option for procedural sedation in pediatrics [49].

13.11.4.2 Lidocaine Infusions

Intraoperative and postoperative intravenous lidocaine has been shown to reduce postoperative pain and opioid requirements. Data demonstrates that the benefit of lidocaine lasts more than 8 h after discontinuation of the infusion, despite lidocaine

having a half-life of about 90 min. The mechanism of lidocaine's analgesic effect is felt to be through anti-inflammatory effects through blocking the priming of neutrophils preventing the release of additional inflammatory cytokines and reactive oxygen species. However, data thus far suggests that the benefit of lidocaine may be significantly greater in certain types of surgeries, notably abdominal procedures [51].

Studies looking at abdominal procedures have used an initial bolus dosing ranging from no bolus to 2 mg/kg followed by an infusion ranging from 1.5 to 5 mg/kg/h. The infusions were continued until the end of surgery or up to 48 h postoperative. Infusion doses greater than or equal to 2 mg/kg/h were associated with decreased pain scores and opioid consumption within the first 24 h. Doses less than that showed no benefit. Infusion extending up to 8 h postoperative showed a reduction in opioid requirements [51]. Furthermore, the effects of lidocaine are more prominent in laparoscopic procedures compared to open. According to a systematic review looking at 45 randomized-control trials, lidocaine reduced NRS pain scores by 1.1 points (CI −1.5 to −0.8) in laparoscopic procedures and by 0.7 points (CI −1 to −0.5) in open procedures [51, 52]. Additional benefits include reduction in PONV and time until return of bowel function. These effects may be mediated through lidocaine's opioid reduction [51, 52].

Perioperative lidocaine infusions have been successfully used as part of an ERAS protocol for colorectal surgery. Details of the protocol are shared in Fig. 13.6. It included a 1 mg/kg bolus at induction, an intraoperative infusion at 2.4 mg/kg/h, and a postoperative infusion at 30–60 mg/h that was discontinued on POD2. This protocol demonstrated improved pain scores, reduced opioid consumption, and decreased length of hospital stay.

Risk of local anesthetic systemic toxicity is exceedingly rare at the infusion doses discussed above. Plasma serum concentrations remain well below the toxic level of 5 mg/cc [51]. However, it must always be considered when patients endorse suggestive signs and symptoms such as tinnitus, perioral numbness, and arrhythmias.

Significantly fewer studies have been performed on the use of lidocaine in other types of surgeries. Albeit few, these studies have shown benefits in prostatectomies, mastectomies, thoracic surgeries, and major spine surgeries. To further validate these initial findings, more research is needed to corroborate these findings before supporting routine use of lidocaine infusions in these patients [51].

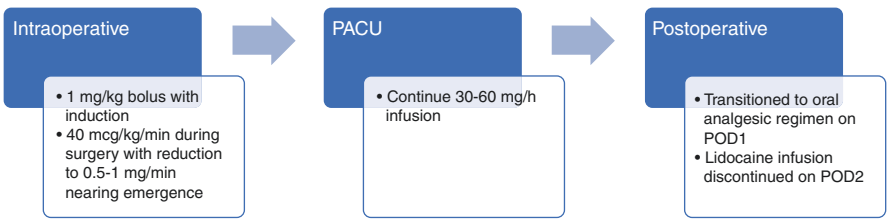

Fig. 13.6 Perioperative lidocaine infusion have been used successfully for analgesia in ERAS protocols. This pathway describes a regimen used at one particular institution [22]

13.11.4.3 Dexamethasone

Dexamethasone is widely used for its antiemetic effects with administered doses typically ranging from 4 to 8 mg. Yet, its effects on pain is less well understood. A systematic review from 2011 looked at the effect of a one-time bolus of dexamethasone on the postoperative pain scores and opioids requirements. The results from 24 randomized-control trials were stratified into three groups: low dose (≤0.1 mg/kg), intermediate dose (0.11–0.2 mg/kg), and high-dose (≥0.21 mg/kg). The findings showed that that intermediate and large doses by had an equivalent analgesic effect compared to placebo and low doses. Thus, it may be advantageous for providers to administer intermediate dose dexamethasone as part of multimodal analgesia [53].

However, the analgesic benefits will need to consider the risks associated with higher-doses of dexamethasone such as impaired wound healing, systemic and wound infections, and hyperglycemia. A meta-analysis published in 2019 looked at a total of 37 studies to identify risks associated with a one-time dose of dexamethasone. They found no change in the risk of wound or systemic infection, or delayed wound healing regardless of dexamethasone dose. However, both of these are uncommon events and a larger sample size may be needed to detect an effect. The study did find an increase in postoperative glucose levels. The mean difference between those receiving dexamethasone and control groups was 13.3 mg/dL in the first 12 h after surgery and 21.2 mg/dL at 24 h after surgery. The study did not separate hyperglycemia results according to steroid dose. The authors of this meta-analysis note that a majority of the studies excluded diabetic patients, who are at greatest risk for infection, impaired wound healing, and hyperglycemia. Thus, these results should not be extrapolated to that population [54].

One retrospective study specifically focused on the effect of low (4 mg) and moderate dose (8–10 mg) dexamethasone in diabetic patients on postoperative hyperglycemia. The study showed that the glucose increased by 9 mg/dL more in the moderate dose group compared to the low dose group in PACU and by 25 mg/dL over the first 24 h. A significantly higher percent of moderate dose patients had a blood glucose >180 mg/dL (74% versus 54%) and a higher percent needed to be dosed sliding scale insulin in PACU (36% versus 25%). Although these findings are statistically significant, the clinical significance of these findings are unclear and will need to be considered with the analgesic benefits [55].

13.11.4.4 Dexmedetomidine

Dexmedetomidine is an alpha-2 adrenergic agonist that targets the large number of receptors in the dorsal horn to provide sedation, anxiolysis, and analgesia. Studies have shown that a continuous intraoperative infusion of dexmedetomidine at 0.5 mcg/kg/h reduced 48-h opioid consumption without worsening of pain scores. Other studies have suggested that it reduced length of stay in the PACU and opioid consumption in the PACU. Thus far, there have not been any studies specifically looking at the effects of dexmedetomidine in the chronic opioid user population [56].

13.11.4.5 Esmolol

Esmolol is an ultrashort-acting beta-1 receptor antagonist. For many years, its primary use has been for the treatment of supraventricular tachycardias. In the past 5 years, many studies have drawn interest to esmolol's ability to modulate pain sensation and reduce opioid requirements perioperatively. A systematic review published in 2018 looked at 23 studies looking at the effect of intraoperative esmolol on opioid requirements and pain [57].

The results demonstrated that patients receiving intraoperative esmolol required less opioids both intraoperatively and postoperatively without having a negative effect on pain scores. The effect size of esmolol was similar to other commonly used opioid-sparing agents such as gabapentin, acetaminophen, and dexamethasone. As this is a relatively new area of research, the studies lacked homogeneity. Thus, a definitive conclusion cannot yet be drawn about the ideal dose of esmolol. The dosing varied widely from 0.5 to 2 mg/kg boluses followed by continuous infusions ranging from 5 to 500 mcg/kg/min [57].

13.11.4.6 Other Modalities

Tylenol, NSAIDs and gabapentin continue to be widely used as part of multimodal analgesia. Benefits of these will not be discussed in detail here.

13.12 Inpatient Management and Initiating OUD Pharmacologic Treatment

Inpatients with acute or chronic pain conditions and OUD are in a unique setting where MOUD can be initiated. Transition to opioid agonist treatment can help manage pain and OUD. Whereas patients with acute and chronic pain conditions are tapered from opioids given concerns about long-term efficacy and risk for complications, patients with OUD should be transitioned to MOUD to reduce risk of relapse, misuse of opioids, and provide needed stability and treatment.

Currently there are three FDA-approved medications for OUD: methadone, buprenorphine, and extended-release injectable naltrexone. All patients with OUD not on pharmacologic management should be recommended one of these treatment options and connected with outpatient substance use treatment [58, 59]. The choice of treatment should be a shared decision between the clinician and patient. Inpatient psychiatric and substance use disorder specialists can assist in this process with careful consideration to the patient's preferences, previous treatment, and setting of treatment (supervised opioid treatment program versus outpatient office setting for buprenorphine or naltrexone). Individuals with a history of diversion, failed outpatient buprenorphine management, and high-risk comorbid substance use might benefit more from a supervised opioid treatment program with

daily monitoring [58]. Patients declining pharmacotherapy for OUD should be provided with outpatient referrals for substance use treatment and an intranasal naloxone kit upon discharge. Although all effective treatments, there are specific considerations and limitations in the inpatient setting surrounding each OUD medication discussed below. Clinicians should reference Figs. 13.7 and 13.8 to guide in their decision-making when starting an inpatient on MOUD. Figure 13.7 is for the patient on a non-opioid pain regimen and Fig. 13.8 is for the patient on an opioid-based pain regimen.

13.12.1 Methadone

Patients who are interested in initiating methadone for MOUD may benefit from methadone as an opioid analgesic for pain conditions, although there are limitations. Dosing will be more frequent every 68 h for analgesic effects and will need to be reduced to once daily dosing as opioid agonist treatment in the outpatient setting, which can be a challenging transition [58]. Prior to discharge, patients must be connected with a federally certified opioid treatment program that will provide methadone, which can also be a barrier if treatment spots are unavailable at the time of discharge. Additionally, these programs often request collaboration in dosing protocols to assure seamless transition to starting doses at the methadone clinic. Opioid treatment programs dispense opioid agonist treatments (more commonly methadone) and provide daily supervised dosing. It is often easier to transition to buprenorphine while inpatient if patient is amenable and then refer to outpatient buprenorphine prescriber.

13.12.2 Buprenorphine

Buprenorphine is an effective treatment for OUD and pain management. In settings where pain cannot be adequately controlled then a full agonist therapy may be indicated. The inpatient setting provides a unique opportunity for rapid induction on buprenorphine. If pain management is not severe, initiation of buprenorphine as the initial pain regimen is ideal for those interested in initiating MOUD. Individuals on a different opioid pain regimen will need to enter a state of mild to moderate withdrawal before undergoing buprenorphine induction. Given buprenorphine's higher affinity for mu-opioid receptors, patients will experience precipitated withdrawal if insufficient time has elapsed since their last dose of opioids. Patient should be in mild to moderate withdrawal or a COWS score of 11–12 or greater [60]. Withdrawal symptoms can be managed with alpha-2 adrenergic agonists (clonidine, lofexidine), antidiarrheal medications, anxiolytics, and sleep aids. It is crucial to symptomatically manage opioid withdrawal as subjective pain might increase and limit comfort in transition to buprenorphine.

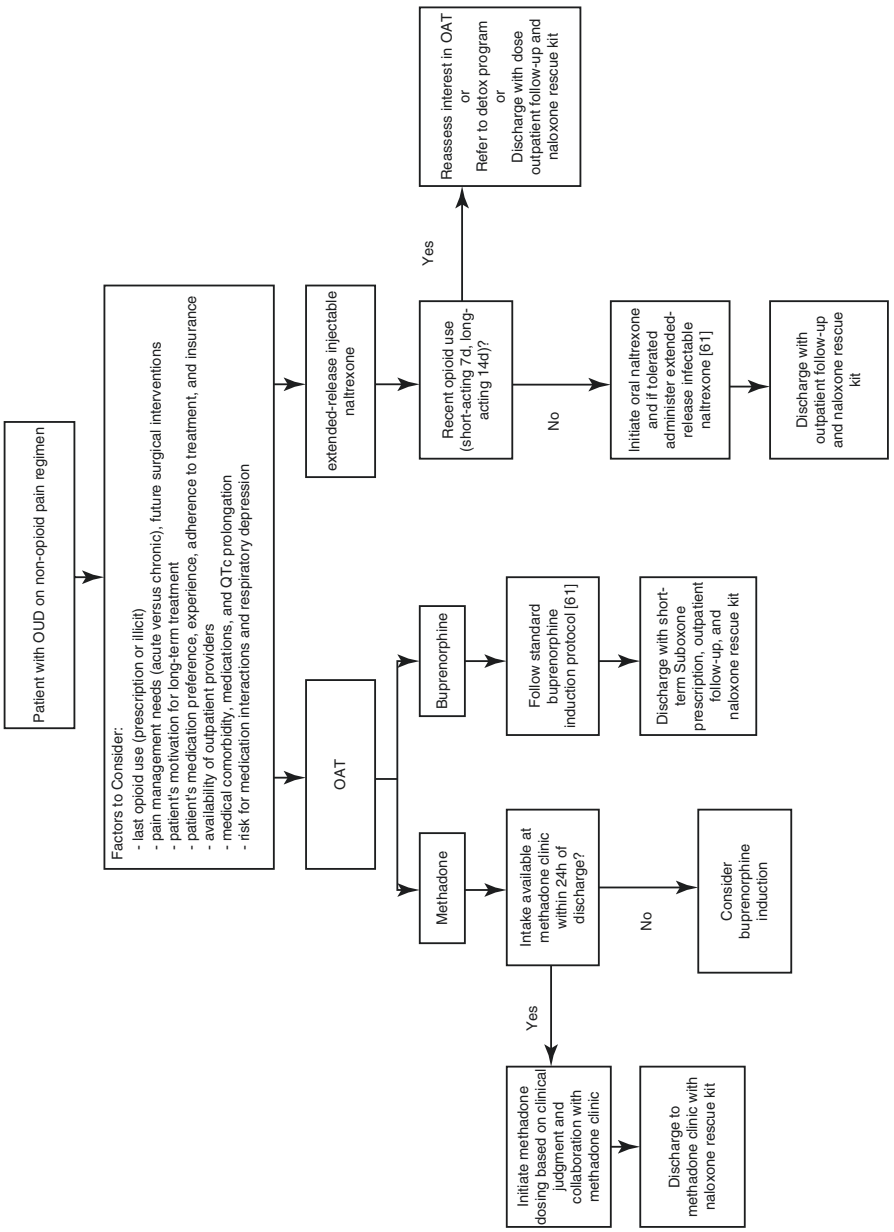

Fig. 13.7 Algorithm for initiating OUD pharmacologic treatment in the patient on non-opioid based pain regimen [58, 59]

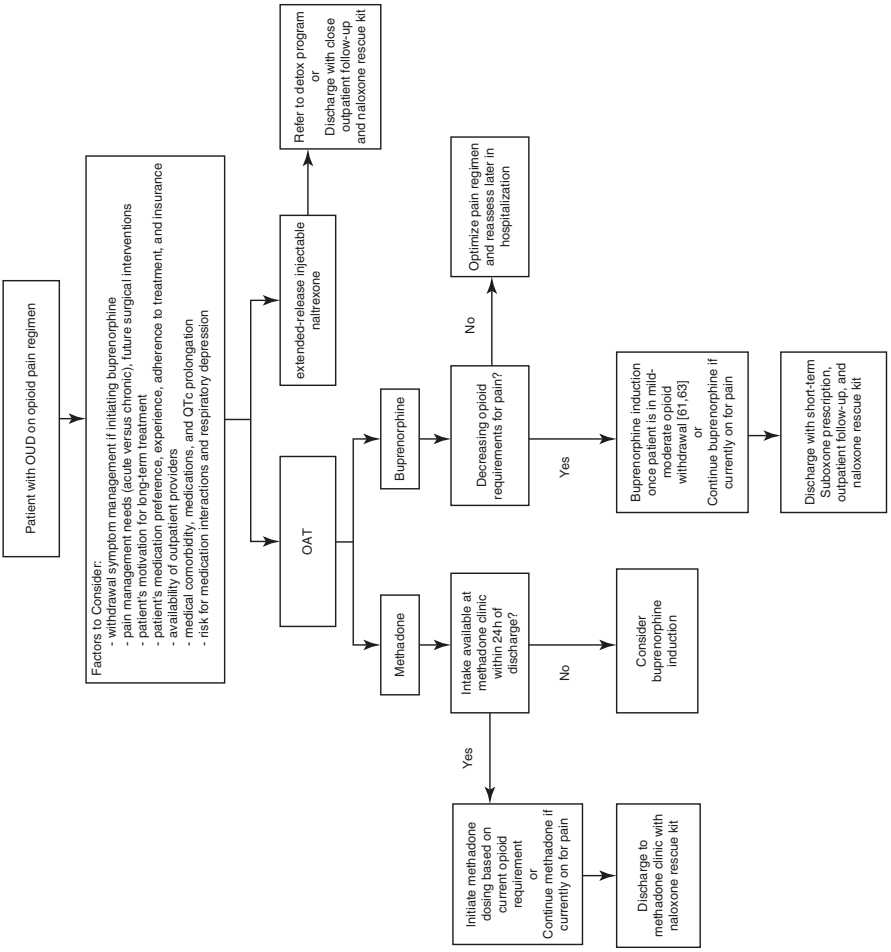

Fig. 13.8 Algorithm for initiating OUD pharmacologic treatment in the patient on opioid pain regimen [58, 59]

Buprenorphine initiation should occur at least 6–12 h after last use of short-acting opioids, or 24–72 h after last dose of long-acting opioids. Once patient is in mild to moderate withdrawal, an induction dose of 4 mg can be initiated and then the patient is observed for 60–90 min. If the patient does not experience worsening withdrawal symptoms, then additional dosing can be done in 2-4 mg increments. The buprenorphine dose can then be increased rapidly to a dose that provides stable effects for 24 h and is clinically effective [58]. While most hospital formularies only have buprenorphine product, patients should be discharged on the combination product (buprenorphine-naloxone or Suboxone®). The naloxone component deters injection and prevents misuse. All patients undergoing buprenorphine induction need immediate follow-up with a buprenorphine provider. Providers may be limited, as prescribers must have a special waiver to prescribe buprenorphine for OUD.

Limitations in buprenorphine induction while inpatient include intolerance of withdrawal symptoms, abbreviated length of stay, medical comorbidities needing further acute management, and need for ongoing acute pain management. Adequate pain relief should always be prioritized, and if unable to initiate buprenorphine inpatient then patients should be connected with outpatient treatment.

13.12.3 Naltrexone

Extended-release injectable naltrexone in the inpatient setting is limited to those whose pain is managed with non-opioid analgesics and individuals not on opioids for 7–14 days. There are current studies looking at more rapid induction methods although not yet widely practiced [61, 62]. This timeline is often a barrier to initiating extended-release injectable naltrexone, and it is not widely available on hospital formularies. For those who have been off opioids for this timeline, an oral naloxone challenge can be useful before initiating naltrexone treatment. A dose of 0.4–0.8 mg of naloxone is administered and the patient is observed for precipitated withdrawal [58]. Careful consideration should be given to those interested in outpatient follow-up for extended-release injectable naltrexone as individuals will need to abstain from opioid use for an extended period of time and are at high risk for relapse and overdose.

13.13 Managing the Patient in the Emergency Department

Patients with OUD frequently present to the emergency department for general medical conditions or complications related to opioid use. Managing a patient with chronic opioid use or OUD in the emergency department can be challenging. Initial workup should be done to diagnose the underlying etiology for the patient's pain. Some considerations in this patient population include soft-tissue infections, opioid overdose, opioid withdrawal, and trauma [63]. The two most common indications for admitting intravenous drug-users to the hospital are pneumonia and soft-tissue infections [63], both of which can both present with sepsis.

If the diagnostic workup rules out any other indications for admission, the pain provider will need to determine if the patient needs to be admitted for pain management. This should be done in close communication with the patient's outpatient provider and their comfort with managing the patient's pain in the outpatient setting. Often times these patients will be sent to the ED directly by their outpatient pain provider for evaluation for inpatient pain management. This can be in the setting of an acute exacerbation or potentially a device-malfunction. If the outpatient provider and patient are comfortable with outpatient management, the patient may be discharged with a short-term opioid regimen. Additionally, ED presentations are another opportunity for pain providers to connect patients with appropriate outpatient providers.

Patients with OUD should be engaged in substance use treatment in the ED. Buprenorphine induction in the ED setting has been shown to effective in increasing patient engagement in treatment compared to brief intervention and referral alone [34]. Initiation of buprenorphine in acute settings can decrease emergency room visits, increase completion of medical treatments, and improve engagement in outpatient substance use treatment [64, 65]. Other MOUD (methadone and extended-release injectable naltrexone) are less feasible in acute ED presentations. Methadone requires linkage to an outpatient federally certified opioid treatment program with immediate follow-up. Extended-release injectable naltrexone is an option in patients who have not received opioids for pain management or used otherwise for 7–14 days. This timeline is often a barrier to implementing in the acute setting. Patients declining MOUD while in the ED need early follow-up with outpatient substance use treatment and should be discharged with an intranasal naloxone rescue kit.

13.14 Naloxone and Discharge Planning

All patients discharged on daily opioid dosing greater than 90-mg morphine equivalents, those on longer-acting opioids (methadone or extended-release oxycodone), and those with a history of OUD or substance misuse should be discharged with an intranasal naloxone kit [24]. Patients at high risk for opioid overdose and those with OUD also need early follow-up with substance use treatment. Substance use treatment includes MOUD, counseling and other supportive services, and is offered by treatment programs or providers in the outpatient setting. It is encouraged to involve family members and significant others in education and training in naloxone administration prior to discharge.

13.15 Summary

- Opioid prescriptions have increased dramatically over the past 20 years contributing to the opioid epidemic. Currently, opioid analgesics are the most commonly prescribed medication in the United States and greater than 2.4 million individuals have OUD.

- Opioid use leads to many physiologic changes that lead to tolerance, dependence, and opioid use disorder.
- The three FDA-approved medications for treatment of OUD are methadone, buprenorphine, and extended-release injectable naltrexone (Vivitrol®).
- Methadone should be continued and naltrexone should be discontinued in the setting of acute pain.
- Literature is still unclear on best management of buprenorphine in the setting of acute pain.
- Multimodal analgesic strategies should be optimized in this patient population due to their increased opioid tolerance and increased perception of pain.
- Ketamine and lidocaine infusions can safely be used as non-opioid analgesics, even in non-monitored settings.
- Only about 20% of OUD patients are on MOUD.
- The inpatient setting may be an ideal time to transition these patients onto MOUD.
- The choice of treatment should be a shared decision between the clinician and patient.
- Close planning and coordinating follow up is vital to preventing risk of relapse after discharge from the hospital.

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Chapter 14
Patient in Rehab and on Buprenorphine/ Methadone/Naltrexone/Naloxone

Andrew J. Wendahl and Keth Pride

14.1 Introduction

With the admission of any patient using opioid agonist therapy (OAT), there exists the dynamic challenge of managing pain control. This challenge amplifies in the context of a surgical or trauma-related patient and is one that inpatient and emergency department providers are faced with on a daily basis. Acute pain management in patients receiving opioid agonist or maintenance therapy is therefore best achieved utilizing a multimodal treatment plan that is individualized to each patient. The majority of the available literature in this area comes from the perioperative management of opioid-tolerant patients.

14.2 Pathophysiology

Prior to effectively treating this patient population, it is important to understand the reason and pathophysiology behind OAT. Proper opioid agonist treatment can allow patients to return to a productive and satisfying lifestyle that was previously unattainable. Although patients treated with opioid agonists are physically dependent, they typically do not have the problematic behaviors and patterns often associated with addiction [1]. Opioid agonists suppress cravings and withdrawal

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symptoms by blocking the acute effects of other opioids. Oftentimes, in order to achieve success with OAT, a slow taper is required sometimes lasting many months. Treatment plans can be optimized by utilizing a clear tapering schedule, providing access to withdrawal medications, and emphasizing the importance of patient engagement.

There are both biological and clinical reasons for difficulty in treating pain in opioid tolerant patients. Central sensitization, tolerance, and opioid induced hyperalgesia are well known reasons for this challenge. The mechanism behind central sensitization is thought to occur by amplified synaptic firing of pain signals from the nociceptor terminal to the dorsal horn neurons; the NMDA receptor is thought to be integral to this process. Chronic stimulation of opioid receptors producing increased sensitivity to pain has been described through mechanisms other than the NMDA receptor including upregulation of spinal dynorphin, activation of protein kinase C, and apoptosis of spinal dorsal horn neurons [2]. Central sensitization has been found to be implicated in both opioid tolerance as well as opioid-induced hyperalgesia.

14.3 Assessment/Evaluation and Identification of Population at Risk

The first step in evaluating a patient with uncontrolled pain receiving chronic OAT is to obtain a careful history and physical examination, and then consider diagnostic studies. Is this pain an exacerbation of the baseline pain or a different pain? The differential diagnosis should remain broad and must also include new drug interactions that decrease the efficacy of current pain medications and also the possibility of an increasing tolerance to current medications.

It should also be noted that an exacerbation of a psychiatric disorder has the potential of increasing the patient's pain experience. Due to the increased prevalence of psychiatric disorders in the chronic pain patient population, a psychological assessment should also be included in the initial evaluation [3, 4].

14.4 Misconceptions That Limit Treatment of Acute Pain in Opioid-Tolerant Patients and Patients on OAT

There are misconceptions surrounding opioid and opioid agonist therapy that may lead to prejudice toward patients. The opioid prescribing climate has changed drastically over the last decade as the 'opioid epidemic' has been publicized and politicized. Consequently, patients that fall into the category of opioid tolerance, addiction, and previous addiction are often viewed under suspicion and perceived as drug-seeking. It is understandable that this population would be more demanding of pain medication, given their fear of being under-treated or that discontinuation could lead

to withdrawal. It is therefore even more important that patients on opioids and opioid agonist therapy receive careful clinical assessment for objective evidence of pain [5].

Four common *misconceptions* resulting in under-treated postoperative pain were identified by Coluzzi et al. and are quoted below. These misconceptions are widespread and can be extremely deleterious to the effective treatment of inpatients on OAT. Therefore, they are extremely important to consider whenever treating any patient or inpatient on OAT [6].

1. "**Maintenance therapy with buprenorphine or methadone provides analgesia.**

   Additional opioid dose is required in patients on maintenance therapy with an opioid agonist for the following reasons:

   (a) Methadone and buprenorphine effect on pain suppression is shorter (4–8 h) than the duration of their effect on opioid withdrawal (24–48 h) [7].
   (b) Due to opioid cross-tolerance, patients require higher and more frequent doses of opioid analgesics to achieve adequate analgesia [8].
   (c) OIH may counteract the analgesic effects of opioids [9].
   (d) These patients display increased sensitivity to natural and experimental pain. Consequently, pain scores are usually higher and decrease more slowly [10].

2. **Additional opioids for analgesia may cause addiction relapse.**

   There is no evidence that analgesic opioids will exacerbate addictive disease. Two small studies suggest that patients on maintenance methadone programs receiving opioids, either for cancer pain or for post-surgical pain, showed no relapse when matched with patients receiving maintenance methadone therapy only [11, 12]. Conversely, due to the potential stress induced, unrelieved pain is a risk factor for relapse among the addicted patients [13].

3. **Additional opioids for analgesia may cause respiratory and CNS depression.**

   Clinical experience does not support this concern. Conversely, there is evidence that tolerance to opioid-related respiratory and CNS depression is protective in acute or worsening chronic pain. Typically, cancer patients who require additional opioids do not exhibit drug toxicity when the dose is escalated. Moreover, inpatients' response to opioids can be monitored [14].

4. **PCA is inadequate for post-surgery analgesia in opioid-tolerant patients.**

   There are no specific guidelines available to address pain-relief interventions in this specific population. Nonetheless, a multimodal approach is recommended [15]. When regional analgesia is not applicable, a PCA system can be considered especially for those who are unable to maintain their oral opioids in the perioperative period [16]. Pain scores in opioid-tolerant patients are higher and decrease more slowly. Opioid tolerance significantly affects analgesic requirements. Unrelieved pain is a risk factor for relapse among patients recovering from abuse. PCA is the only system which allows to provide patients with the right

dose of opioid, according to their effective needs [17]. However, the appropriate setting of bolus size and lockout interval may be challenging, despite the risk of opioid-related respiratory depression being low in opioid-tolerant patients [18]."

14.5 General Recommendations for Pain Management in Patients Using OAT

Whether the patient is taking buprenorphine, methadone, naltrexone or bup/nal, certain treatment options should be considered in order to optimize pain control in this patient population. With such limited research, the following guidelines are based on the available literature, pharmacologic principles, and published recommendations.

- Discuss pain management plan with patient in nonjudgmental manner so as to minimize and prevent consternation and pain-related anxiety.
- Reassure patient that their addiction history will not prevent sufficient pain management.
- Continue the usual (or equivalent) dose of OAT [19].
- Use conventional analgesics, including opioids, to aggressively treat pain.
  - In all cases, because of variable interpatient opioid metabolism and unpredictable buprenorphine dissociation from the mu receptor, naloxone should be available and level of consciousness and respiration should be frequently monitored [20].
- Opioid cross-tolerance and an increase in pain sensitivity often necessitate higher opioid doses administered at shorter intervals [19].
- Write continuous scheduled dosing orders rather than as-needed dosing.
- Avoid using mixed agonist and antagonist opioids because they can precipitate acute withdrawal syndrome [20].
- Whether the patient is opioid tolerant or naive, on buprenorphine or methadone, multimodal treatment modalities should be utilized that simultaneously target pain pathways at different sites using different mechanisms. This approach to pain management is associated with superior pain relief and decreased opioid consumption [21].

14.6 Buprenorphine

Mechanism—Buprenorphine is a semisynthetic opioid derivative of thebaine, a naturally occurring alkaloid of *Papaver somniferum*, or opium poppy. It has a high binding affinity for the mu-opioid receptor, effectively competing with other opioids that bind to the same receptor. It functions as a partial mu-opioid agonist such that

when it binds to the receptor, it mimics the pharmacological effect of an opioid but to a much lesser extent, thus preventing opioid withdrawal symptoms. Another unique characteristic of this drug is that it has a slow rate of dissociation from the receptor, producing a prolonged duration of action compared to other opioids [22]. It is also a full kappa-opioid receptor antagonist contributing to its dysphoric and psychotomimetic effects.

Additional Characteristics—Buprenorphine has also been shown to reverse opioid-induced hyperalgesia (OIH) through "buprenorphine-induced antinociception." [23] Normally, opioid exposure increases spinal dynorphin, an endogenous kappa-receptor *agonist*, which can contribute to OIH. Buprenorphine, as previously stated, is a kappa-receptor *antagonist* that can compete with the effects of spinal dynorphin resulting in decreased OIH [24].

Maintenance Therapy/Dosing regimens—Recommended starting doses of the approved formulations for opioid naive patients with chronic pain are 75 mcg buccal buprenorphine once daily or every 12 h, or 5 mcg/h via transdermal patch. As is recommended with all opioids, it should be titrated slowly and incrementally so as to avoid side effects. In one study on low back pain, opioid naive patients required 150–450 mcg buccal twice daily to provide adequate analgesia [25]. Maximal doses are 900 mcg buccal and 20 mcg/h transdermal.

14.7 Managing Acute Pain, Inpatient

The treatment of acute pain in patients taking buprenorphine is particularly challenging. Its high receptor-binding affinity, long half-life, and partial mu-receptor agonism may inhibit the effects of traditional opioids potentially resulting in poorly controlled postoperative pain and serious adverse events [26, 27]. With such limited empirical data, the following treatment approaches for patients on buprenorphine requiring opioid analgesics are based on the available literature and pharmacologic principles, specifically those published by Alford et al. in their 2006 article published in the Annals of Internal Medicine.

In this patient population, four different options exist and should be chosen based on the patient's anticipated duration of pain, the current treatment setting, and the patient's response to chosen treatment.

1. If short duration of pain expected, continue usual dose of buprenorphine and titrate short-acting opioids for breakthrough pain [28].
2. Divide buprenorphine dose to every 6–8 h to optimize its analgesic properties. For example, the available literature suggests that acute pain can be effectively managed with as little as 0.4 mg sublingually every 8 h in opioid-naive patients [29].
3. Discontinue buprenorphine maintenance therapy and treat pain with full opioid analgesic therapy by titrating to effect and then to achieve analgesia. Convert back to buprenorphine only when acute pain no longer requires additional opioid therapy [28, 30].

4. If longer duration of pain expected, discontinue buprenorphine therapy and treat opioid dependence with methadone 20–40 mg/day, a dose that will prevent acute withdrawal in most patients [31]. Due to the decreased binding affinity of buprenorphine for the mu receptor, responses to additional opioid agonist analgesics should be more predictable and effective. Manage additional pain by titrating short-acting opioids. When acute pain has resolved, discontinue methadone and convert back to buprenorphine prior to hospital discharge [32].

14.8 Managing Acute Pain, Perioperative

Given the limited data regarding the clinical outcomes of patients taking perioperative buprenorphine, TA Anderson et al. at the University of Michigan Health System created a protocol published in Anesthesiology titled "To Stop or Not, That is the Question: Acute Pain Management for the Patient on Chronic Buprenorphine." Based on pharmacology, published reports, and clinical experience, this author agrees with its findings and endorses its recommendations which are illustrated below (The buprenorphine patch was not included in this protocol) [33]. Of note, this algorithm may also be used as a guideline when treating acute pain in the non-surgical inpatient.

- In the protocol created by TA Anderson et al., perioperative management of a patient taking buprenorphine is largely split up into two treatment arms: elective or emergent surgery. Under the elective surgery arm, postoperative pain and opioid requirements should be anticipated as being either minimal or significant. If minimal postoperative pain is expected, then the patient should stay on their current dose and supplement with non-opiate adjuncts. If the patient has recently stopped their buprenorphine, then the surgical team should identify the daily dose, confirm time since discontinuation, and consider postponing surgery until buprenorphine has been completely metabolized and its effects minimized. If the following time-interval criteria can be met, then treat with traditional opioids using opioid-tolerant dosing.

  - 0–4 mg per day—stop ×24 h before surgery
  - 4–8 mg per day—stop ×48 h before surgery
  - 8–12 mg per day—stop ×72 h before surgery
  - >12 mg—preoperative management plan per buprenorphine provider

- If moderate or severe postoperative pain is anticipated and the patient is still taking buprenorphine, then the surgery should be canceled or postponed until the aforementioned time-interval criteria have been met allowing for the complete metabolism of buprenorphine. Communicate with the patient's buprenorphine provider to develop a plan to wean the patient off buprenorphine prior to surgery. This should include the institution of a short-acting opioid to bridge pain control in the preoperative period. A plan for follow-up and reinstitution should also be

confirmed. If buprenorphine is successfully stopped prior to surgery, then expect opioid requirements to be similar to opioid-tolerant patients. Ensure appropriate outpatient follow-up and consider additional non-opiate adjuncts.

- Under the urgent/emergent surgery arm, the surgical team should again assess anticipated postoperative pain and opioid requirements. If minimal pain is expected then the surgical team should alert the prescriber, continue the buprenorphine for postoperative pain, consider adjuncts, and minimize supplemental opioids. If the patient has stopped their buprenorphine, then assess time since discontinuation. If greater than or equal to 5 days off, then treat with traditional opioids and expect tolerance.
- If the surgery is expected to elicit moderate to severe pain, then buprenorphine should be discontinued. A PCA should be initiated which will likely require high-dose opioid infusion—preference should be given to high dose PCA over high-dose basal rate. Consult the acute pain service as well because this management will require close monitoring. Additionally, schedule acetaminophen, consider gabapentin or pregabalin, continuous regional catheter, and dexmedetomidine for ICU patients, and continue traditional opioid therapy for postoperative pain upon discharge. Coordinate follow-up with buprenorphine provider for planned opioid wean and reinstitution of buprenorphine therapy. If patient was off buprenorphine prior to urgent/emergent surgery then anticipate the patient's course to be similar to a tolerant patient.

Communication with prescribing physician—When an acute pain episode arises, it is imperative to have an *early* discussion with the patient's buprenorphine provider to ensure that appropriate support is in place. Creating a clear analgesic care plan for after discharge can help to prevent confusion, reassure the patient, and avoid the psychological stress of poorly treated pain. If a new opioid agonist is indicated for pain, a plan for its safe use should be developed with the outpatient provider in order to ensure adequate pain control and avoid complications. In the surgical setting, devising a pain management plan should begin in the preoperative assessment and should include a collaborative multidisciplinary approach incorporating a pain management specialist, mental health professionals, and, again the opioid agonist prescriber.

Evidence—Currently, there is no consensus or high-level evidence describing acute pain management techniques for inpatients on buprenorphine.

Risk—Concerns while taking this medication include CNS depression impairing physical or mental abilities and caution should be taken while operating any machinery or performing tasks requiring alertness. In patients at higher risk of hepatotoxicity transaminases should be monitored prior to and during therapy. As with other opioid agonists, the patient should be closely monitored upon drug initiation or dosage escalation for risk of respiratory depression. Misuse via self-injection, CNS depressant co-administration (i.e. ETOH or benzodiazepines) may exacerbate respiratory and CNS depressant effects. Hypersensitivity and hypotensive episodes have been reported [34]. Buprenoprhine has also been observed to cause QTc prolongation and should be avoided in patients with personal or family history of prolonged QTc or those taking other medications known to prolong the QTc interval [34].

The risks and benefits of continuing buprenorphine or any of the following opioid agonists in the perioperative period should be explicitly discussed with patient. Again, an individualized treatment plan, preferably developed in cooperation with the patient, is essential to providing optimal pain control.

14.9 Methadone

Mechanism—Methadone is a racemic mixture of two stereoisomers (L- and D-methadone) with L-methadone being 8–50 times more potent than D-methadone and pharmacologically more active [9]. It is an antagonist at the glutamatergic N-methyl-D-aspartate receptor as well as a full agonist at the mu-opioid receptor [35]. Its action at the NMDA receptor is likely responsible for its benefit in the treatment of neuropathic pain. Lastly, it also inhibits reuptake of serotonin and norepinephrine.

Characteristics—Methadone has a long and unpredictable half-life (13–58 h). After oral administration, it can be detected in the bloodstream after 30 minutes and has a bioavailability ranging from 41 to 95% such that serum levels vary greatly [36].

Maintenance Therapy/Dosing regimens—Methadone is dosed daily in methadone maintenance treatment (MMT) because of its average half-life of 15–40 h. The maintenance dose of oral methadone begins with initial oral doses of 15–30 mg, usually increased to the most effective dose between 80 and 120 mg daily [37].

Managing Acute Pain—HCPs managing acute pain in patients on MMT should refer to the aforementioned general recommendations for pain management for patients using OATs. Additional inpatient and perioperative recommendations for patients in MMT are included below [32]:

1. If the patient is able to tolerate oral medications, oral methadone should be continued on the morning of surgery and through perioperative period.
2. If oral medication is not tolerated, then the methadone dose can be given parenterally (intramuscular or subcutaneous) at a dose half to two thirds the maintenance dose divided into two to four equal doses a day. The relative analgesic potency ratio of oral to parenteral methadone is 2:1, with wide variability due to its pharmacodynamic and pharmacokinetic properties.
    (a) An example: In a patient taking 80 mg oral methadone daily, the IM dose would be 10–13 mg every 6 h or its equivalent every 12 h.
3. Practical rules to convert methadone to morphine
    (a) Unfortunately, methadone conversion is challenging because conversion calculations are bidirectional.
        (i) Most studies have investigated the conversion dose ratio in patients going from morphine to oral methadone, showing that methadone is more potent in patients on high-dose opiates (i.e. when going from high dose opiates to methadone, less methadone is required).

(ii) The estimated dose ratio for IV methadone to oral morphine equivalent daily dose (MEDD) is 13.5. The estimated dose ratio for oral methadone to oral MEDD is 4.7.
(iii) When oral methadone is converted to IV morphine sulfate, estimated dose ratio is 2:1.
(iv) The ratios may vary largely depending on patient metabolism, including the effect of CYP inducers and inhibitors.
(v) Usually 2–3 days are required to achieve a stable dose.

(b) Example

(i) In a patient taking oral methadone at 80 mg daily, the equivalent IV dose of morphine would be 40 mg daily.
(ii) In opioid naive patients, the IV morphine dose can be reduced to 20–30 mg daily (i.e. continuous infusion of 1 mg/h or 24 mg per 24 h), only for maintenance therapy [38].

Communication with prescribing physician—The patient's methadone maintenance program should be notified at both the time of admission and discharge in order to verify methadone dose, inform program clinical staff of any controlled substances given to the patient are detectable by urine drug screen, and lastly to coordinate follow-up for eventual reinstitution and management of methadone therapy.

Evidence—Currently, there is no high-level evidence describing acute pain management techniques for inpatients on methadone.

Risk—Methadone interacts with other medications frequently and, like buprenorphine, is known for causing QTc interval prolongation, resulting in possible significant cardiac toxicity and life-threatening arrhythmia. At higher levels, it can also cause hypoxia and severe pulmonary edema, particularly when mixed with benzodiazepines [39].

14.10 Naltrexone

Mechanism—Naltrexone is a pure opioid antagonist, used in patients with opioid and alcohol dependence. It is a cyclopropyl derivative of oxymorphone similar in structure to naloxone and nalorphine (a morphine derivative). It has its highest affinity for mu receptors. Its efficacy is mediated through interactions between dopamine and endogenous opioid neuropeptide systems, also involved in the expression of reinforcing effects of alcohol [40].

Maintenance Therapy/Dosing regimens—The new once-monthly extended-release formulation of injectable naltrexone prevents the relapse to opioid dependence following detoxification [41]. Per Up to Date dosing guidelines:

- Oral: Initial: 25 mg; if no withdrawal signs occur, administer 50 mg/day thereafter; alternative maintenance regimens may be used and include: 50 mg on

weekdays with a 100 mg dose on Saturday; 100 mg every other day; or 150 mg every 3 days (degree of blockade may be reduced with extended dosing interval regimens and doses >50 mg may increase risk of hepatocellular injury).

- IM: 380 mg once every 4 weeks.

Managing Acute Pain—These patients present a challenge for practitioners treating patients with acute pain. Naltrexone may cause reduced sensitivity to opioids or precipitate withdrawal symptoms when naltrexone is re-dosed soon after opioid use [42]. Patients may remain refractory to or more sensitive to opioids. A patient may remain refractory to opioid-induced analgesia within the first 2 weeks. By the fourth week the receptor antagonism may be overcome by high dose opioids. This occurs because chronic opioid antagonism results in increased density of opioid receptors in the brain.

It has been recommended that treatment in these patients be non-opioid focused to include NSAIDs and acetaminophen, corticosteroids, ketamine, and regional analgesia. Oral naltrexone should be discontinued at least 24–72 h prior to opioid based care [43]. For the above reason, if possible, elective surgery should be scheduled during the fourth week following naltrexone initiation. In the case of emergency, consider high dose opioid analgesic treatment, appropriately titrated.

Perioperative management [44]:

- Discontinue oral naltrexone at least 72 h before scheduled elective surgery if opioid use is anticipated.
- Extended-release IM naltrexone should be discontinued at least 30 days prior to scheduled surgery (oral naltrexone may be used temporarily).

Communication with prescribing physician—It is pertinent to communicate with the prescriber for regarding patients on suspected naltrexone therapy with a questionable history. If naloxone therapy is considered, a challenge test may be helpful to confirm that the patient is opioid-free as a urine drug screen may not be sufficient proof. Patients in transition from buprenorphine or methadone may be vulnerable to withdrawal symptoms for up to 2 weeks. For acute and emergent pain management, it is prudent to consider alternatives to opioids. If opioid therapy is required, patient care should be provided under the direct supervision of a trained anesthesia provider.

Evidence—There is limited evidence available on perioperative management of patients undergoing treatment with naltrexone. Most of the literature is in case reports noting pain refractory to the effects of opioid agonists. It has been recorded that there may potentially be hypersensitivity due to receptor up-regulation.

Risk—Risk of accidental opioid overdose with high dose opioid management is present, primarily due to the increased density of opioid receptors in the brain as previously described. This type of patient may also respond to lower opioid doses than expected. It is important for the patient to be aware that this increased sensitivity still exists after treatment is discontinued, after a missed dose, and near the end of the dosing interval. Naltrexone may also precipitate symptoms of acute withdrawal in opioid-dependency. This could present as pain, hypertension, sweating,

agitation, and irritability. Dose-related hepatocellular injury has also been reported with the margin of safety between appropriate dosing and hepatotoxic doses being approximately five-fold. Therefore, transaminases should be also monitored for elevation. Abrupt discontinuation could also lead to acute liver injury. Lastly, suicidality and depression have been reported necessitating close patient monitoring and awareness throughout the therapeutic period [34].

14.11 Buprenorphine–Naloxone (Bup/Nal 4:1 Ratio, Suboxone)

Mechanism—See buprenorphine mechanism above. Naloxone is a short-acting, broad opioid receptor antagonist. It binds to opioid receptors with high affinity and becomes a competitive antagonist of opioid receptors. When administered at low doses, naloxone can reverse opioid side effects such as respiratory depression, sedation, and hypotension without fully reversing analgesia. At high doses, naloxone can precipitate opioid withdrawal [45]. It is 45% protein bound, rapidly metabolized by glucuronidation to naloxone-3-glucuronide in the liver, and excreted primarily in the urine.

Maintenance Therapy/Dosing regimens—It remains unclear as to whether bup/nal maintenance therapy is superior to methadone maintenance therapy, which has been the standard of care for opioid addicted patients. The studies are mixed in terms of superiority. One study suggests bup/nal might be even more effective than methadone in reducing opioid consumption and preserving cognitive function [46]. Other studies suggest that methadone is more effective at reducing opioid use and retaining patients in the maintenance therapy [47].

Managing Acute Pain—Limited data exist on the optimal acute pain management strategy in these patients. The concern with agonist/antagonist therapy is the drug's high affinity for mu-opioid receptors, potentially blocking other opioids from activating the receptor. Patients on bup/nal therapy are expected to require a higher dose of opioids during the acute pain period, therefore, a standard opioid-based plan may not be sufficient [48]. Ongoing bup/nal therapy may need to be replaced with other opioids as soon as possible during the acute pain period. If the choice is made to replace bup/nal preoperatively with other opioids, then its postoperative reinstatement should be managed carefully and in cooperation with the drug's original prescriber. The presence of buprenorphine in the drug and its effect on the mu-receptor create an elevated but indeterminate opioid requirement for pain control [49]. We therefore refer the provider to the aforementioned summarized recommendations by Alford et al. and Anderson et al. that describe the respective inpatient and perioperative management of a patient on baseline buprenorphine therapy.

Communication with prescribing physician—Except for urgent and emergent situations, buprenorphine transitions should be handled by a specialist in the field. Abrupt discontinuation in a highly stressful, and emotionally charged scenario, such as the perioperative period, risks precipitation of opioid use disorder relapse [50].

Evidence—A randomized clinical trial comparing bup/nal to methadone in opioid dependent patients found that treatment retention rate and analgesic effect did not differ between drugs. It also found that while methadone was more effective at reducing illicit opioid use, bup/nal showed a greater improvement in mood, energy, personality, and the psychological component of chronic pain [47].

Risk—See risks associated with buprenorphine medication as stated above. Additional risks associated with the administration of naloxone include acute opioid withdrawal and all its associated symptoms including increased pain, tachycardia, hypertension, and irritability [34].

14.12 Special Considerations: Indications for Use Opioid Agonists Outside of Opioid Use Disorder

There is minimal published data or studies showing the efficacy of buprenorphine/naloxone (bup/nal) for pain relief in non-opioid dependent patients with chronic pain [22]. The weak analgesic effect of buprenorphine in the form of bup/nal is unlikely to provide adequate pain relief for patients without opioid dependence or addiction. In low doses, buprenorphine can only partially activate the mu-opioid receptor. In moderate doses, its opioid agonist effect reaches a plateau or ceiling such that any further dose increase is unlikely to enhance analgesia. There exists a similar ceiling effect, however, for opioid-induced ventilatory impairment. In high doses, it actually functions as an opioid antagonist thus limiting its analgesic effect [51]. Given its low addictive potential and favorable safety profile, the role of bup/nal as both an analgesic and addiction management tool continues to grow [52].

Methadone has been studied for its use in the perioperative setting due to its unique pharmacokinetic profile. Randomized clinical trials have shown that when compared to shorter-acting intraoperative opioids, methadone is associated with greater reductions in postoperative analgesic requirements. Risk of opioid-related side effects were also not increased in the methadone groups in any of the investigations [44]. In the summary below, per the 2009 Opioid Treatment Guidelines, the following recommendations were given for Methadone use as chronic opioid therapy in chronic non-cancer pain:

Clinicians who prescribe methadone should be familiar with its complex clinical pharmacology and associated risks (ie. QTc prolongation and cardiac arrhythmias). Use of methadone for chronic non-cancer pain (CNCP) has increased dramatically, however, few trials have evaluated the benefits and harms. Based on panel consensus, a safe starting dose in opioid-naive patients is 2.5 mg every 8 h, with no more frequent than weekly dose increases. More cautious and slow dose titrations are recommended for older patients or those with renal or hepatic comorbidities. In opioid-tolerant patients, convert to methadone cautiously. Equianalgesic dose ratios are variable and can range from 0.1 to 10% morphine equivalents (lower at higher doses). It is recommended that patients on low dose opioids to be treated as opioid

naive patients while initiating methadone. In patients on higher dose opioids, methadone should not exceed 30–40 mg a day. Multiple methods have been described for dose titration, however, given its complex pharmacokinetics none are strongly recommended with evidence. Methadone is not recommended for breakthrough pain or prn use for the above reasons [53].

14.13 Summary

- Managing patients on opioid agonist therapy can represent a dynamic challenge for any health care provider.
- In order to optimize pain control in the inpatient setting in this patient population, please recall the four misconceptions and refer closely to general guidelines as listed in prior sections.
- Optimizing acute pain management in opioid tolerant individuals using OAT requires diligence, careful monitoring, and appropriate use of multimodal analgesia.
- Fortunately, we can look to perioperative literature on guidance in treating new onset pain, but additional studies are required to better understand the most effective treatment course for individuals using opioid agonist therapy in an inpatient setting.

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Chapter 15
The Elderly with Dementia

Sook Kyung Yoon and Peggy Y. Kim

15.1 Introduction

Globally, our population is increasingly aging. Population aging is defined as a mass shift in the distribution of a country's population towards older ages. The year 2015 was a monumental year, when the number of people aged 65 or older outnumbered children under age 5 [1]. The World Health Organization (WHO) has predicted that the number of elderly people (conventionally defined as >65 years of age) worldwide will reach 1.5 billion by 2050, up from 900 million in 2015 [1, 2]. With the burst in growth of older adult patients, the need to manage acute and chronic pain in older patients in the inpatient setting is becoming more common. As the population ages, the number of older people who experience dementia will also increase [3]. Dementia is a progressive, neurological disease that leads to a permanent loss of cognitive abilities. Approximately 4.5–8% of people over 70 and 15–64% of people over 80 will experience dementia [3].

Pain is equally prevalent in the elderly with dementia as it is in the cognitively intact elderly population [4]. Although there are wide variations in estimates, a recent systematic review found that 46–56% of older people with dementia experience pain [5]. It has also been shown that regardless of the type of dementia (i.e., Alzheimer's, vascular dementia, frontotemporal dementia, etc.), reported pain levels appear to be similarly affected. Despite widespread pain in this population, studies have shown that those with dementia are less likely to be treated with analgesic medications than their cognitively intact counterparts [6–8]. This phenomenon is partly due to difficulties in assessing pain as well as clinicians' false assumptions that pain is part of the natural course of aging [4].

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There are several challenges in treating pain in the elderly with dementia. First of all, the effective treatment of chronic pain in any patient requires a thorough and accurate assessment of pain. Assessment of a patient's functional status, including mobility, sleep, weight changes, mood, and cognitive impairment is also necessary. If the patient is able to respond appropriately verbally and has mild to moderate cognitive impairment, assessing pain via simple questioning is possible [9]. However, if the patient has severe cognitive impairment, he or she may not be verbal and it may be impossible to make these inquiries. Second, the elderly population has associated complex biopsychosocial, environmental, and economic factors that clinicians must consider when treating their pain. As people age, they experience common age-associated psychosocial phenomena, such as the loss of family and friends and the loss of independence, which can contribute to pain and suffering [4]. Noticing such nonuniform, nonlinear, and heterogeneous changes across different facets of a patient's life can provide valuable insight when assessing pain as well as assist in better informing the provider or caregiver in choosing nonpharmacologic and pharmacologic treatments [4]. Third, age-related physiologic changes may have potential pharmacokinetic consequences. With aging, various organ systems undergo tremendous changes in their composition and function, affecting the bioavailability of medications. In general, it is crucial to hold true to the old adage of "start low and go slow" in this population. Finally, the average elderly person has multiple comorbidities, and the risk of significant polypharmacy (defined as greater than five medications) is elevated [10]. As it is well documented in the literature and well-known among geriatricians, polypharmacy correlates with increased morbidity (e.g., falls, delirium, loss of function), as well as mortality [10–13].

The treatment of pain in this fragile population should always begin with nonpharmacologic strategies to attempt to reduce polypharmacy. Engaging different disciplines such as physical therapy, occupational therapy, and social work will also help address the multidimensional aspects of pain, even in an inpatient setting. Topical pharmacologic agents should be considered prior to systemic medications. Interventional methods for the treatment of pain should be discussed, potentially to be performed either in the inpatient setting or in an outpatient setting subsequent to discharge, after exhausting all conservative management. Most importantly, improving the quality of life, optimizing functional independence, and minimizing disability in older adults should be the goal of all treatments [14].

15.2 Pathophysiology

15.2.1 Age-Related Changes Relevant to Pain

The perception of pain among the elderly is affected by physiologic changes at multiple levels. In the peripheral nervous system, the impaired function of nociceptive nerves may result from a loss of integrity or decreased density of cellular

elements. Substance P and calcitonin gene-related peptide concentrations diminish over time. In the central nervous system, there is a reduction in several critical elements of neurotransmission (e.g., endorphins, gamma-aminobutyric acid, serotonin, norepinephrine, opioids, and acetylcholine) [15], which results in improper pain signal transmission and neuromodulation [14]. Evidence also suggests that there is a decrease in the number of dopaminergic neurons and receptors with aging [14]. This results in dysfunction of the descending modulatory pathways of the spinal dorsal column, which normally serves as an endogenous pain inhibitory system [14].

A large meta-analysis by Gibson et al. suggests that among older adults, pain thresholds increase and pain tolerance decreases [14]. The pain threshold may vary based on the type, duration, and location of the stimulus. Older adults experience increased pain with the application of heat stimuli at shorter durations at peripheral or visceral sites, as compared with adults in general. On the other hand, older adults experience less pain with mechanical pressure and ischemia [14]. In conclusion, pain may not serve as a reliable warning sign of tissue damage due to more atypical clinical presentations in conditions such as cardiac ischemic pain and abdominal pain.

15.2.2 Age-Related Physiologic Changes and Potential Pharmacokinetic Consequences

As we age, we develop physiologic changes that likely result in altered pharmacokinetic consequences. Pharmacotherapy for older adults is vastly different than in the younger population. The reasons for this include but are not limited to: physiologic changes due to aging, including limited medication clearance; multiple comorbidities; reduced physiological reserve; polypharmacy; and dementia [16].

People's body compositions undergo changes as they age. The aging process leads to a relatively catabolic state with reduced anabolic influences, which is thought to cause sarcopenia. Sarcopenia is the loss of muscle mass and strength with age, and is often accompanied by an increase in fat mass and abdominal girth. Adipogenicity increases and serum albumin decreases in the elderly, which lead to the higher accumulation and longer half-lives of fat-soluble drugs, decreases in water-soluble drug distribution, and increases in insulin resistance and metabolic dysfunction [16].

Medications that have a high hepatic extraction ratio may undergo decreased clearance and increased half-life in older adults because of diminished liver size and decreased blood flow [9]. In addition, the number of functional glomeruli decreases over time, resulting in a decrease in renal clearance at a rate of 6.3 mL/min/1.73 m^2 per decade. The remaining nephrons develop age-related nephrosclerosis, which leads to less kidney function reserve [9].

Opioid sensitivity increases with the associated decline in mu opioid receptor density and increase in opioid affinity in the elderly. This explains why older adults tend to respond to opioid doses that are significantly smaller than those used in younger individuals [16] (Table 15.1).

Table 15.1 Age-related physiologic changes and their implications

Categories	Age related physiologic changes	Implications
Body composition [16]	↑ in adipogenicity ↓ in muscle mass ↓ in body water content ↓ in serum albumin (20%)	Accumulation and longer half-lives of fat-soluble drugs ↓ distribution of water-soluble drugs Altered protein binding and increased risk for drug interactions ↑ insulin resistance, metabolic dysfunction
Liver function [16]	↓ in size by 25–35% ↓ in hepatic blood flow of more than 40%	↓ metabolism of hepatically cleared drugs, lower extraction ratio ↓ first-pass metabolism of some drugs
Kidney function [5]	↓ number of functional glomeruli ↓ in GFR at a rate of 6.3 mL/min/1.73 m^2 per decade ↑ age-related nephrosclerosis	↑ susceptibility to acute kidney injury ↓ in water-soluble drug excretion ↓ kidney function reserve
Central nervous system [15]	↓ number of myelinated and unmyelinated fibers ↓ in nerve conduction velocity ↑ in blood–brain barrier permeability	↑ susceptibility for extrapyramidal effects of antipsychotics ↓ proprioception ↑ postural instability, balance deficits, and falls ↑ vulnerability to central side effects
Pain modulation system [15]	↑ sensitization of pain with ↓ pain inhibitory system activity	↑ sensation of pain
Peripheral pain fibers [15]	Deterioration of structural, functional, and biochemical changes of peripheral nerves	Altered pain perception

15.3 Diagnosis

When assessing pain, obtaining a comprehensive history and performing a thorough physical exam is essential. Pain is an unpleasant sensory and emotional experience, well defined by Melzack and Wall and subsequent researchers [17, 18]. Thus, assessment should address both the physical and psychological aspects of pain. Before interviewing the patient and assessing his or her cognitive abilities, there are several neurologic changes in the elderly that clinicians should consider. Aging is associated with decreased brain volume, frontal gray matter loss, and decreased cerebral blood flow. Brain activity shifts from the posterior to the anterior regions, and cortical thinning develops, as well [19]. With age, there is a decline in episodic memory, and people have more difficulty recalling the "what," "where" and "when" of various events. Retention of new information, processing speed, multitasking ability, task shifting capabilities, and executive functioning

may also decline with age [19]. In contrast, procedural and semantic memory is usually stable with aging, but declines in people with dementia. This significant difference distinguishes pathologic dementia from the normal aging process.

First, a careful assessment of the patient and removal of elements that may limit pain assessment is crucial. The elderly population commonly experiences diminished sensory perception, including losses of hearing, eyesight, and taste. With aging, senses such as vision become increasingly impaired due to retinal aging, optic nerve damage, and lens aging, leading to non-correctable decreases in visual clarity and acuity, haloes, and poor night vision. In addition, eyesight in the elderly is more likely to be affected by medical conditions such as macular degeneration or glaucoma, and to be diminished by the consequences of their other comorbid conditions, such as diabetes. Age-related hearing loss is another common condition that occurs in the elderly, with intrinsic (cochlear aging) and extrinsic (noise exposure, ototoxic drugs) factors that influence the incidence and prevalence of such deficits [20]. Without hearing aids and glasses or other appropriate assistive devices, patients cannot function at their maximal capabilities, and may appear to be more cognitively impaired than they actually are [21] (Fig. 15.1).

Prior to assessing pain in the elderly with dementia, it is important to assess their cognitive ability and function. Ensuring that the elderly patient has appropriate assistive devices such as hearing aids and glasses will help minimize errors in pain assessment. As patients with dementia may have limited semantic (often pathological due to dementia) or episodic (decreased as a part of normal aging) memory, it is a good idea to involve the patient's healthcare power of attorney (POA) and/or family members when acquiring details regarding the patient's history and when planning treatment. Involving various disciplines such as physical therapy, occupational therapy, social workers, speech therapy, psychologists, and spiritual leaders of a patient's religion, if applicable, are likely to provide additional helpful dimensions to consider in assessing and treating pain in this vulnerable population.

Clinicians should always assess other modifiable factors that can exacerbate pain and appropriately address them when they can. These factors may include, but are not limited to poor sleep quality, smoking, bowel and bladder incontinence, and depression [14]. Poor oral intake from eating hospital food that is unpalatable or unfamiliar to the patient, such as strict low sodium and/or low fat diets, or dysphagia/lack of coordination which often accompanies the later stages of dementia, can also heighten the experience of pain.

The assessment and treatment of comorbid conditions are also important in the diagnosis and treatment planning of pain in the elderly. Other comorbidities should be addressed in parallel, as their optimization can often improve pain control. Depression screening is important, as this comorbidity is common in patients with pain and can go unrecognized and remain undertreated in older patients. In addition, the psychomotor manifestations of depression can make the diagnosis of dementia more challenging. The Patient Health Questionnaire 9 (PHQ 9) is one quick, easy depression assessment tool, but there are many others that can be used.

Diagnostic imaging and ancillary tests in the elderly with dementia should only be considered based on indications from a thorough history and physical examination,

Fig. 15.1 Symptoms of dementia

given the increased incidence of abnormal but potentially incidental findings in asymptomatic older adults [18]. In addition, such additional investigations may be uncomfortable, invasive, or difficult for the patient to comply with, so these tests should only be undergone if their outcomes are likely to change the patient's treatment plan or management.

15.4 Treatment

When choosing a treatment modality, it is necessary to understand that elderly patients with dementia have varying limitations in their ability to consent. It may be necessary to involve their healthcare POA and their family in these discussions.

15.4.1 Non-pharmacological Management

Inpatient physical therapy (PT) is a vital part of treatment planning for the elderly with dementia. Elderly patients are already predisposed to Type 2 nerve fiber decline as a normal part of aging, as mentioned above. This peripheral nerve fiber loss accelerates if an elderly patient is restricted to bedrest. In older adults, 10 days of bed rest can result in a decrease of 11–12% of muscle strength per week. PT can provide individualized exercise treatment that can decrease the risk of falls and fall-related injury, and prevent muscle mass loss and joint contracture. In general, 10–30 seconds of static stretches and 3–4 repetitions for each stretch is recommended for maintaining flexibility if there are no contraindications [22].

Assistive devices or orthoses can be helpful for the treatment of pain in the elderly. PT and occupational therapy (OT) can aid clinicians in choosing which devices would be beneficial and can help educate patients regarding how to appropriately use these devices. For example, a single-point or quad cane can be used to take some weight off a painful hip and provide additional stability in ambulation [22]. A walker can provide stability and allow the patient to off load some weight from their lower extremities [22]. The temporary, intermittent use of back braces can be helpful in ameliorating intractable back pain. Limited abdominal binder use can be helpful in posture correction and pain relief in some patients with chronic axial back pain. Flexion limiting spine orthoses such as Cruciform Anterior Spinal Hyperextension (CASH) or Jewitt braces can be helpful for discogenic or vertebral body compression fracture pain. Between the two braces, CASH braces tend to be a better option, as this type of brace provides more flexibility with less rotational limitation of the lumbar spine and allows the limbs to move freely. Other noninvasive modalities such as transcutaneous electrical nerve stimulation (TENS) units can be helpful in pain improvement. TENS units stimulate the alpha delta fibers to block the painful C fiber ascending pathway of pain [17].

Music therapy is a great adjuvant non-pharmacological tool for the management of chronic pain [23–26]. It is non-invasive, inexpensive, and easy to implement; therefore, it is an attractive option. The most accepted hypothesis of music-induced analgesia is its effect on the descending pain modulatory system [23]. Music characteristics such as high familiarity [27], few beats-per-minute [24], and self-chosen music [25] have been reported to elicit cognitive and emotional mechanisms such as distraction [26], pleasure [27], sense of control [23], and beneficial placebo-like effects [27, 28], all of which can affect the descending pain modulatory system, which, in turn, may contribute to the analgesic effect of this treatment modality. In a recent systematic review and meta-analysis by Garza-Villarreal et al., 14 randomized controlled trials (RCTs) were analyzed. This meta-analysis found that music reduced self-reported chronic pain and depressive symptoms; this positive impact was greater when the patient chose the music [29].

Sleep is often interrupted in inpatient settings. Tang et al. monitored sleep and pain reports over the course of a week in a sample of 119 mixed chronic pain patients in their natural living and sleeping environments using actigraphy and electronic daily diaries to assess sleep, pain and mood reports at three time points per day [30, 31]. Sleep quality was a significant and consistent predictor of next day pain at all assessment points [32]. A systematic review of longitudinal studies illuminated a general decline in sleep quality and quantity, which was associated with an increased risk of developing a pain condition, small elevations of inflammatory markers, and a reduction in self-reported physical health status [33]. Therefore, it is important to properly educate health care providers, nurses, ancillary staff, and other members of the health care team to make every effort to improve the chances for increasing patients' restorative sleep. The nursing staff should avoid waking the patient at night and limit interruptions besides those clinically necessary, such as checking patients' vitals and drawing time-sensitive labs. Sleep hygiene can also be improved by instituting policies to turn off lights and televisions at night, minimize talking in the hallways or at nursing stations near patient care areas, set visiting hours to allow for sufficient patient rest, and limit the number of allowed visitors per room.

Psychological support for the elderly is vital to successful pain management, even in the inpatient setting. The elderly have many life adjustments, including losses of family, friends, jobs, and physical function. If these critical life changes are not adequately addressed, they can lead to depression [22]. In addition, living with chronic disease and illness can be correlated with increased depression, and health crises/hospitalizations are often associated with increased stress from the burden of potentially coming to terms with new diagnoses or worsening function. Social work and psychology services are important in assisting patients in managing these life changes and helping patients develop coping strategies (including pain coping strategies and pain education), even in the hospital. For example, giving up a driver's license due to a diagnosis of moderate dementia can be a devastating way to lose one's independence, but it can be more tolerable if the individual is provided support and education regarding available transportation services [22].

15.4.2 Pharmacological Management

Topical analgesics. Topical analgesics may be considered in conjunction with non-pharmacological management. These include lidocaine 5% patches or ointment/cream, topical nonsteroidal anti-inflammatory drugs (NSAIDs) in a patch or gel, and capsaicin (cream/gel or 8% patch). Age-related skin changes include thinning of the epidermis, decreased cell replacement, impaired immune response and wound healing, and decreased moisture content, elasticity, blood supply, and sensory sensitivity [31]. These changes increase the risk of developing skin injuries. Also, elderly dementia patients can easily forget to take off patches (which is less of an issue in the inpatient setting). Therefore, clinicians need to ensure a safe way to apply the medication and educate both patients and caregivers. Lidocaine 5% patch and 1–5% lidocaine cream are effective, FDA-approved medications for postherpetic neuralgia, but are often used to treat a multitude of pain conditions. Systemic lidocaine levels remain within a safe range with doses of up to four patches within 24 h. The patch is contraindicated in advanced liver failure and patients receiving oral class I antiarrhythmic medications (e.g., mexiletine).

Topical NSAIDs, including topical aspirin, indomethacin, diclofenac, piroxicam and ketoprofen have mixed results in improving neuropathic and non-neuropathic pain syndromes, according to the Cochrane Data base systemic review by Derry et al. [34] Systemic absorption appears to be minimal when these agents are used in recommended doses, and thus there is more flexibility in using these preparations in patients who may not be candidates for oral NSAIDs due to renal or other comorbidities, or who have difficulties in swallowing, as in patients with advanced dementia [35].

The capsaicin 8.0% patch provides some benefit in the reduction of neuropathic and non-neuropathic pain, although 30% of patients may not be able to tolerate the burning sensation associated with treatment initiation [36]. Applying an 8.0% patch for 30–60 min (after the administration of a local anesthetic at the intended site) has shown to provide pain relief that starts within a few days and persists for 3–6 months after a single application [36]. However, it is only FDA approved for neuropathic pain as a result of post-herpetic neuralgia, and it may be difficult to obtain for other pain conditions.

Other compounded topical medications can be considered, as well, such as topical ketamine, baclofen, amitriptyline, or gabapentin. However, there is limited evidence of efficacy in the literature (possibly secondary to the lack of standardized dosing). In addition, they can be costly to obtain, as they must be made in a special compounding pharmacy and may take a few days to compound for patient use.

Nonopioid analgesics. Acetaminophen is no longer a first line agent for osteoarthritis induced pain. However, it may be an option for pain treatment in patients with mild to moderate pain and moderate to severe renal impairment, as NSAIDs are contraindicated in this population. Acetaminophen has been shown to be particularly effective in treating certain pain conditions such as headache [37]. In the inpatient setting, IV acetaminophen has been used as a supplemental pain agent after

surgery. Hypotension is a potential side effect of IV acetaminophen [37]. The suppository form of acetaminophen can also be useful in older adults with severe dementia and/or dysphagia. However, the elderly often have liver dysfunction due to the physiologic changes of aging, and there is an additional risk for liver toxicity if this medication is incorrectly dosed. Clinicians must assess patients for other risks that may increase their hepatic insufficiency, including chronic alcohol abuse or dependence, prior to administering the medication. Also, a careful current medication list review for combination opioid medications with acetaminophen should be undertaken, to avoid overdosing of this medication.

NSAIDs are a widely used class of drugs for the treatment of mild-to-moderate pain. Although they differ from one another in chemical class, all inhibit the synthesis of prostaglandins. This inhibition can lead to renal insufficiency or gastrointestinal injury in the elderly. The elderly are at a higher risk of these adverse effects due to the physiological changes associated with aging. In one study of adults 65 years of age and older, NSAIDs were implicated in 23.5% of the study's cases of adverse drug reactions resulting in hospitalizations [38]. NSAIDs are also associated with an increased risk of serious cardiovascular events, including myocardial infarction [39], stroke, and congestive heart failure episodes, for which elderly patients are already at risk.

There are a few considerations when selecting nonselective COX inhibitors for pain relief. Naproxen sodium has the least cardiovascular toxicity in this group. Diclofenac sodium has increased COX-2 inhibitor selectivity, so theoretically has less GI bleeding risk. However, it has a higher cardiovascular risk compared to other traditional NSAIDs. Nabumetone has a relatively long half-life and there are minimal antiplatelet effects associated with this agent as compared to other NSAIDs when used for longer than 5 days. Ketorolac has a high potential for adverse gastrointestinal and renal toxicity, and therefore is inappropriate for long-term use, especially in the elderly. According to Bally et al., even short-term use of NSAIDs for 8–30 days at a high daily dose (e.g., diclofenac > 100 mg, ibuprofen > 1200 mg and naproxen > 750 mg) are associated with increased harm [39].

Selective COX-2 inhibitors (diaryl heterocyclic NSAIDs) can be considered as a first-line oral pain medication in the elderly with dementia, if the patient does not have pre-existing gastrointestinal issues (e.g., GI bleeding) or renal dysfunction. Celecoxib has a similar risk of cardiovascular events as naproxen or ibuprofen, but it is safer with respect to a reduced number of serious gastrointestinal events (PRECISION study) [40]. A meta-analysis of observational studies found that celecoxib was not associated with an increased risk of cardiovascular events at doses lower than 400 mg per day. It is important to note that the time period of greatest cardiovascular risk occurs during the first week of use. Short term use for 8–30 days at a high daily dose of celecoxib (>200 mg) is associated with the greatest harm. Rofecoxib, which was withdrawn from the worldwide market due to its increased incidence of cardiovascular adverse effects, conferred a greater than 100% increase in risk for acute myocardial infarction [39].

Other routes of administration of NSAIDs, such as IV ibuprofen and IV or intramuscular (IM) ketorolac, are options for some patients with moderate acute pain in

the inpatient setting. However, as with the oral route, contraindications for the use of IV/IM NSAIDs include any history of renal dysfunction, gastrointestinal (GI) bleeding, recent surgical bleeding, platelet abnormality, congestive heart failure, cirrhosis, asthma, concomitant angiotensin-converting enzyme inhibitor therapy, or recent cardiac or vascular surgery [41]. Many older adults have at least one of these contraindications, limiting its use in the inpatient setting.

Opioids. When considering opioid administration in this population, it is important to distinguish acute pain from chronic pain. Opioids are no longer considered first line treatment for chronic, noncancer pain, even in the hospital, due to their increased risks of mortality and morbidity in the absence of or only very small benefits noted in the literature, including deterioration of quality of life and long term pain relief. However, in acute noncancer pain or cancer pain, opioids may be appropriate for moderate to severe pain not relieved by acetaminophen, NSAIDs, and other adjunctive medications/modalities, or if there are contraindications to these first-line medications.

Most opioids are metabolized through glucuronidation oxidation, except morphine, oxymorphone, and hydromorphone. These medications are considered to have a high hepatic extraction on first-pass metabolism. Morphine, in particular, is then metabolized by the liver to morphine-6-glucuronide (active metabolite) and morphine-3-glucuronide (inactive metabolite with potential neurotoxic effects), which are cleared renally within 24 h [42]. With renal insufficiency (<30 mL/min), accumulation of these metabolites can lead to oversedation and respiratory depression, therefore morphine should be avoided in patients with significant renal impairment [42]. Meperidine is sometimes used in the inpatient setting to reduce shivering after anesthesia and to decrease pain. However, it is contraindicated in older adults with renal impairment, because its renally cleared active metabolite can cause seizures [42, 43].

Due to reduced metabolism in patients with liver dysfunction, lower oral doses of opioids are recommended for the elderly. Also, the elderly often have very slow GI motility and frequent constipation due to physiologic changes, and opioids tend to exacerbate these issues, potentially leading to ileus and other GI complications.

With the above considerations, partial opioid agonists (tramadol, buprenorphine, pentazocine, and butorphanol) are an attractive option, as they are associated with a lower risk of constipation and respiratory depression. According to the updated Beers Criteria 2019, tramadol can now be used in patients with chronic seizures or epilepsy [43]. However, it has been noted to have independent risks of causing SIADH, hyponatremia and hypoglycemia [44]. Lee et al. found that the concomitant use of pregabalin and tramadol, a partial opioid agonist, did not appear to exhibit any significant interactions [45].

Opioids are to be used with extreme caution concurrently with benzodiazepines due to the nearly fourfold increased risk of opioid overdose and respiratory depression [46]. There is a black box FDA warning advising against concomitant use of these two classes of medications. However, in the inpatient setting, these medications are occasionally still used together, since there is increased monitoring capability and conditions sometimes warrant providing both of these medications

together (e.g., sedation while intubated on a ventilator, or for end of life care). Also, clinicians should be careful in using gabapentinoids (gabapentin, pregabalin) concurrently with full opioid agonists. When used concomitantly, there is a 49% higher mortality related to opioid overdose [47]. Therefore, patients should be monitored more closely and may need to have their doses adjusted to avoid potential drug overdose [46].

Intravenous opioids remain the mainstay of analgesia for the treatment of moderate to severe acute pain in the inpatient setting. This may also be the route of choice in older adults with severe dementia or dysphagia, for whom an intravenous (IV) or subcutaneous (SQ) infusion is a more commonly used form of treatment for severe pain. Both routes avoid the first-pass effect and can be supplemented by as needed doses for breakthrough pain. The SQ route has a faster onset of analgesia compared with most oral preparations and is a safer route for patients with poor venous access and those with bleeding disorders or reduced muscle mass compared with the intramuscular (IM) route. A common system for delivering IV opioids is patient-controlled analgesia (PCA), most commonly using morphine, hydromorphone, or fentanyl. It is widely used for treating postoperative pain and cancer pain. However, PCAs may not be an appropriate option in patients with moderate to severe dementia, since they may not have the cognitive capacity to adequately utilize this method of pain control.

Alternatives for patients unable to use IV, IM, SQ, or oral preparations of opioids include rectal, sublingual, buccal, intranasal, transdermal epidural, or intrathecal routes of administration. Epidural and intrathecal routes of administration, commonly used in the perioperative, postoperative, obstetric and cancer populations, introduce opioids directly to the opiate receptor-rich neuraxis. These two forms of selective analgesia have the advantage of requiring relatively small quantities of opioids, thereby reducing the risk of central and autonomic complications.

IV fentanyl has a rapid onset (3–5 min), high potency (100 times compared with morphine), minimal effect on myocardial and hemodynamic function, and an absence of histamine-release properties (particularly relevant for patients with bronchospasm). Fentanyl and its synthetic variants (i.e., remifentanil, sufentanil) are highly lipophilic drugs with rapid distribution to highly perfused tissues (e.g., brain, heart, kidney and GI tract) and are not affected by renal or hepatic insufficiencies [48]. The initial equilibration time of fentanyl is 6 min and its elimination half-life is 3–6 h. Therefore, this is a very attractive IV opioid of choice. However, it has potential synergistic effects with coadministration of certain drugs, including anesthetic agents (may cause hypotension) and serotonergic agents (serotonin syndrome), which are common drugs used in older adults.

IV methadone can be used in pain patients, especially in cancer patients or those who were taking methadone prior to admission but are now unable to take oral medications for various reasons. However, it has a variable half-life anywhere from 12 h to 1 week and it can prolong the QTc interval that can lead to life-threatening cardiac arrhythmia [49]. Numerous older adults are already on medications that prolong the QTc. Therefore, a thorough medication evaluation is

needed prior to prescribing this medication to avoid complications such as torsades de pointes.

Antidepressants. Serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and sodium channel blockers (NaSSAs) are often used to treat chronic pain. Duloxetine has been shown to be effective in relieving neuropathic and musculoskeletal pain and to improve quality of life. There are conflicting data for pain relief from venlafaxine according to a Cochrane review [50]. When deemed appropriate, SNRIs are preferred over TCAs, as they do not have significant muscarinic, histamine-related, and adrenergic side effects. However, the drug class is associated with serious adverse events such as bone fractures, cardiac arrhythmia, myocardial infarction, and severe hyponatremia. In a Canadian population-based study, duloxetine was 8 times more likely to cause hyponatremia when used <30 days in patients >65 years of age [51]. Depression/suicidal ideation should be assessed prior to administering duloxetine, as it can provoke suicidal ideation. Duloxetine has also been associated with an increased risk of falls in the elderly, which would be even more concerning in an elderly population with dementia, as patients with advanced dementia already have a significantly elevated risk of falling due to incoordination.

Tricyclic antidepressants (e.g., nortriptyline, amitriptyline and desipramine) should be one of the last medications to consider for the treatment of pain in the elderly with dementia. They have significant adverse cholinergic effects such as blurred vision, dry mouth, constipation, and urinary retention. Moreover, TCAs are associated with frequent falls, increased mortality, and an increased risk of dementia [43, 52]. The secondary amines, nortriptyline and desipramine, tend to have fewer anticholinergic side effects, so they are preferred if a TCA is to be used [16, 43].

Calcium channel blockers/anticonvulsants. Gabapentin and pregabalin are α2δ2 voltage-gated calcium modulators that are frequently used to treat neuropathic pain. However, gabapentin can cause or exacerbate cognitive or gait impairment [43], and as noted above, can increase the risk of sedation, respiratory depression, and overdose when combined with other medications such as opioids. In addition, renal dose adjustments should be made if the patient has significant renal dysfunction. Therefore, careful monitoring, low starting doses, and judicious up-titration are necessary. It is a good idea to start the medication at nighttime. Patients with significant balance or gait issues at baseline, as is often the case in advanced dementia, are not ideal candidates for this medication.

Topiramate, another anticonvulsant, has been shown to reduce the intensity of neuropathic pain and to improve sleep [53]. Unlike pregabalin and gabapentin, it can cause weight loss. Therefore, this may not be an ideal medication for elderly patients with dementia who have an increased risk of weight loss due to dysphagia, other feeding difficulties, and failure to thrive.

Carbamazepine is an anticonvulsant that is used in neuropathic pain management for trigeminal and glossopharyngeal neuralgia and Guillain-Barre syndrome. However, due to its significant potential side effect profile and the need to monitor renal and hepatic function, drug levels for toxicity, and a complete blood count

(CBC) for blood dyscrasias, this medication is infrequently used, especially in the elderly population who may have renal or hepatic comorbidities.

Muscle relaxants. Cyclobenzaprine, tizanidine, dantrolene, and baclofen are four common medications used to treat diffuse myofascial pain. Muscle relaxants can increase the risk of falling, hypersomnolence, and cognitive decline, and thus should be used with great caution in the elderly with dementia. Among the muscle relaxants, dantrolene is the medication least likely to cause hypersomnolence, and cyclobenzaprine is the most likely medication to do so. Dantrolene should be used cautiously in the setting of liver dysfunction. Cyclobenzaprine dosing should be reduced in renal dysfunction.

Pharmacologic considerations in elderly patients. In the presence of hepatic impairment, there are multiple medications that should be avoided or cautiously prescribed [54]. For example, the clearance of NSAIDs with long half-lives (such as celecoxib, naproxen, piroxicam, and sulindac) that are hepatically metabolized may be reduced in older adults [54]. All opioids except morphine, oxymorphone, and hydromorphone are metabolized by CYP-mediated oxidation, which is reduced with liver dysfunction [54]. Therefore morphine, oxymorphone, and hydromorphone have little potential for metabolically based drug interactions [42] while others have substantial drug interaction potential. Tramadol undergoes 80% hepatic metabolism, so it may accumulate faster in the elderly population. Hydrocodone and oxycodone rely on CYP2D6 and 3A4 for metabolism to their active potent metabolites, hydromorphone and oxymorphone respectively [42]. The analgesic effect of these medications may be less potent in patients with liver dysfunction due to decreased conversion to their active metabolites, while decreased clearance and prolonged half-life may produce more unwanted adverse effects. Fentanyl dosing should be adjusted according to renal function. Carbamazepine should be avoided in patients with liver dysfunction.

Analgesics that are affected by aging-associated declines in renal function include codeine, duloxetine, gabapentin, meperidine, pregabalin, propoxyphene, salicylate, tramadol, and opioids (especially morphine, oxycodone, hydromorphone, and methadone). Gabapentin and pregabalin should be adjusted according to renal function [43, 51]. If a patient is on dialysis, gabapentin should be decreased to a one time dose of 100–300 mg only after dialysis, and pregabalin will need supplementary dosing (50% of daily pregabalin dose) in addition to daily dosing. Meperidine is contraindicated in older adults, especially those with renal impairment, because its renally cleared active metabolite can cause seizures.

15.4.3 Interventional/Advanced Options

There are many advanced and minimally invasive techniques which exist for the treatment of pain. However, there are several issues with exploring interventional options. In the inpatient setting, advanced options may include patient controlled analgesia (PCA) pumps, IV infusions, and various percutaneous regional or neuraxial blocks/catheters, depending upon the resources of the hospital.

When utilizing PCA pumps in elderly patients with dementia, it is important to assess for patients' cognitive abilities to use the pump appropriately. Also, clinicians must assess for potential inappropriate use by a caregiver. There have been incidents of a caregiver or family member pressing the PCA button for the patient out of good intentions, which bypasses one of the safety mechanisms for this treatment modality (i.e., if the patient is too sedated to push the button, then they will not receive additional doses), possibly causing accidental overdose. The American Society of Anesthesiologists (ASA) recently published guidelines on the use of IV ketamine in 2018. According to this guideline, there is limited evidence for IV PCA-delivered ketamine as the sole analgesic for acute or periprocedural pain, but it may be a good adjunct to opioid-based IV PCAs (Grade B recommendation, moderate level of certainty) [55, 56].

Intravenous (IV) infusions (lidocaine, ketamine, dexmedetomidine). IV infusion therapy can be an attractive option for patients with mild to moderate dementia who are able to tolerate IV medications and have enough cognitive function to understand the implication of the therapy. Here, we discuss IV lidocaine, IV ketamine, IV propofol, and IV dexmedetomidine therapies, but there are other therapies potentially available. Intravenous ketamine, propofol, and dexmedetomidine are approved by the FDA for acute pain. None of these medications are FDA approved for use in chronic pain.

IV lidocaine is an amide anesthetic, sodium channel blocker that is a Class Ib antiarrhythmic drug. Although intravenous administration of lidocaine for the treatment of pain is not FDA-approved, it has adequate evidence for certain conditions, including postherpetic and peripheral neuropathic pain [57], Complex Regional Pain Syndrome (CRPS) [58], and fibromyalgia [56]. Therefore, it can be considered as a treatment option on a case by case basis. There are various protocols for preservative-free lidocaine infusions, but most agree on an infusion rate of 5 mg/kg lidocaine delivered over 30–60 min intravenously. If patients do not respond to their first dose, an escalation to 7.5 mg/kg may be trialed [59]. This medication can be a useful adjunct for pain control in the hospital, if other modalities are ineffective or cause too many mental status changes or other side effects in this already fragile population. However, lidocaine infusions are relatively contraindicated in patients with chronic alcohol use; certain EKG findings including PR interval > 200 ms, QRS complex > 120 ms, or bifascicular block regardless of QRS complex duration; history of seizure; advanced age/poor functional status; and renal/hepatic dysfunction; or if they are currently taking any antiarrhythmic agents [59]. It is absolutely contraindicated if patient has significant cardiac conduction block or the patient is allergic to the drug or amides [59].

Ketamine, an analog of phencyclidine that antagonizes the N-methyl-D-aspartate (NMDA) receptor, is an older medication that has been used as an analgesic and as a general anesthetic, often in combination with other medications. In chronic pain patients, this treatment has shown moderate evidence for pain relief in CRPS and spinal cord injury [59]. This medication can also be used as opioid taper adjunctive therapy, as well. There are consensus statements and/or guidelines issued by the American Society for Regional Anesthesia (ASRA) [55], the American Academy of

Pain Medicine (AAPM) [60], the American Society of Anesthesiologists (ASA) and the American Psychiatric Association (APA) [61] on the use of ketamine for acute pain, chronic pain, and mood disorders. The patients who are most likely to benefit from perioperative ketamine as adjunctive analgesia include patients undergoing painful procedures, opioid-tolerant patients, patients with obstructive sleep apnea, and patients with sickle cell disease [59]. ASA IV ketamine guidelines state that ketamine should be avoided in individuals with poorly controlled cardiovascular disease, increased intracranial pressure, elevated intraocular pressure and cirrhosis, which are prevalent in the elderly population. Ketamine should be used with caution in individuals with moderate renal impairment, as well, which is also common in elderly patients. In addition, this medication can cause dissociative symptoms and other mental status disturbances, and thus must be used very cautiously in elderly patients with dementia, who already have underlying cognitive challenges.

Intravenous propofol can be used perioperatively for pain relief or for sedation. It is used to treat acute migraine headaches and opioid-induced hyperalgesia. It works via potentiation of the gamma-aminobutyric acid (GABA) receptor. Propofol is roughly 98% bound to albumin, metabolized by the liver, and excreted via the urine [59]. Therefore, older adults with reduced albumin and liver/renal dysfunction will have increased accumulation of the medication. Further, propofol produces venous dilation and causes hypotension, often to less than 50% of preoperative levels. Moreover, it causes decreased level of consciousness and memory loss, due to its effects on the CNS. Therefore, this may not be a first line drug to treat pain in older adults with dementia who are already prone to delirium and mental status issues.

IV dexmedetomidine is a highly selective alpha-2 agonist with analgesic and sedative properties. Due to its alpha-2 agonist effect, it is associated with a higher incidence of bradycardia and hypotension compared with other sedative agents (e.g., midazolam) [62]. It is a weak analgesic by itself, but is a potent potentiator of the analgesic effect of opioids and endogenous enkephalins. Dose adjustment is needed for hepatic impairment, which again is often a limiting factor in elderly patients.

Interventional procedures. Interventional procedures in the hospital can include, but are not limited to, spinal/neuraxial injections/catheters, peripheral nerve blocks (PNB), sympathetic blocks, field blocks, neurolytic and non-neurolytic blocks such as somatic nerve blocks, if such services are available at their facility. Neuraxial interventions can include epidural catheters, which can be dosed with local anesthetic and potentially a low dose of opioid medication. Epidural catheters can provide excellent pain control with greatly reduced medication side effects, especially as compared with oral opiates or other pain medications that can cause sedation and incoordination. However, if the patient has severe dementia and is at risk of self-removing the catheter, this would not be as attractive an option.

PNBs in deep or superficial anatomic locations can be useful for diagnostic and therapeutic purposes. They can be a very attractive non-opioid interventional method of controlling a patient's pain, as they have a lower risk of urinary retention, hemodynamic problems, and postoperative nausea and vomiting than opioids or

other medications [63]. They can be performed as a one-time administration of local anesthetic or an infusion through a perineural catheter (continuous nerve block) and can be placed via ultrasound guidance or nerve stimulator guidance. They are frequently performed perioperatively, but can also be performed as a rescue block or for intractable pain not caused by surgery (e.g., an injury from a fall that is not amenable to surgery). PNBs have been shown to decrease opioid consumption and shorten discharge time in ambulatory settings because of decreased incidence of nausea, vomiting, and severe pain [64]. They may also diminish or prevent the development of chronic pain syndromes due to the decrease of central nervous system sensitization that occurs after an acute injury. Peripheral nerve catheters can also be placed, which dispense local anesthetic near a nerve over a longer period of time (usually 5 days or so). Compared with a single injection nerve block, continuous PNBs are associated with improved pain control, decreased need for opioid analgesics, less nausea, and greater patient satisfaction [64].

However, if a patient has severe or advanced dementia, it is unlikely they would be able to understand the reason for or the steps involved in different interventional procedures, or they may become frightened or be unable to remain compliant with positioning for the procedure. Patients with severe dementia may be more likely to attempt to inappropriately remove peripheral nerve catheters or have them dislodge, which would be suboptimal. Therefore, it is important to assess the appropriateness of each of these advanced modalities based on the individual's cognitive ability and preferences.

15.5 Pain Assessment Tools

The assessment of pain in the elderly with dementia can be challenging. A thorough history should be performed, as mentioned above, as well as a complete physical exam, with particular focus on the patient's painful area(s) (either by the patient's report or by caregivers' observations). Quantifying pain in patients with dementia pose additional difficulties, but studies have indicated that seniors with mild to moderate dementia are capable of providing valid responses to unidimensional self-report measures of pain, such as the 21-point box scale and numeric rating scales such as the Visual Analog Scale (VAS) [9, 15, 65]. A 21-point box scale has a row of 21 boxes labeled from 0 to 100 in increments of 5. The 0 anchor is labeled "no pain," while the 100 anchor is labeled "pain as bad as it could be." To complete the scale, respondents indicate the box that best represents their pain [64].

As patients' cognitive function deteriorates, as assessed by tools such as the Mini Mental Status Examination (MMSE), their self-report of pain becomes less reliable, especially with scores of 18 or less on the MMSE [65]. Manifestations of pain in such individuals vary from lethargy and physical aggression or agitation to grimacing and groaning [66]. For such individuals, vital sign trends, especially signs of sympathetic activation (i.e., tachycardia, hypertension, tachypnea, diaphoresis, piloerection), can be helpful clues in to pain assessment. For more objective measures of

a patient's pain, behavior observational scales would be more appropriate than self-reported scales. There are a considerable number of pain assessment tools available for use with the elderly cognitively impaired population [66]. However, there is limited evidence about their reliability, validity and clinical utility based on a systematic review. On the basis of this review, no one tool can be recommended above all others, given the existing evidence [66]. Among the many different tools available, two commonly used assessments include the Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC) [67] and the Doloplus-2 [68].

The PACSLAC is a checklist developed by Drs. Fuchs-Lacelle and Hadjistavropoulos in 2004 for the purpose of screening pain in older adults with dementia and a decreased ability to communicate. It can be completed by a caregiver based on their observations of the older adult during activity or movement after a day-long shift of observation [67]. The PACSLAC contains 60 items which are separated into four sections: (1) facial expressions; (2) activity and body movements; (3) social, personality, and mood indicators; and (4) physiological indicators, eating and sleeping changes, and vocal behaviors. A dichotomous scale is used to determine if the behaviors are present or absent. The sum of each subsection is tallied, based on the number of behaviors/indicators present within that subsection, and those subsection scores are summed for a grand total. The total PACSLAC score can discriminate between pain and non-pain related distress events [67]. It is a simple, fast and efficient way to assess pain in the elderly with dementia. It can be administered in 5–10 min and its internal consistency is 0.92 with a Pearson correlation coefficient of 0.83 ($p < 0.01$) when completed by a caregiver [67].

The Doloplus-2 is a comprehensive tool for assessing pain in nonverbal elders [68]. A Doloplus-2 assessment is performed by a proxy rater who observes the patient and evaluates the presence of ten pain-related behaviors that comprise three subscales (somatic, psychomotor, and psychosocial). Each behavior is graded from 0 to 3. The observed ten behaviors include: verbal complaints, facial expressions, protective body postures, protection of sore areas, disturbed sleep, functional impairment in activities of daily living (washing and dressing, and general mobility), psychosocial reactions such as behavioral problems, and changes in communication or social life. Authors of the Doloplus-2 suggest a cut-off score of 5 out of 30, indicating that representing pain is possibly being present. Some studies have shown the clinical utility of the Doloplus-2 to detect pain in patients with very advanced age and severe dementia [66, 68]. However, internal consistency and accuracy was not evident in this study, so caution should be used in interpreting the results of this assessment [66].

15.6 Challenges in the Management of Pain While in the Hospital

The main challenges in the management of pain in the elderly with dementia involve the complexity of their comorbid conditions and of pain itself. It is arguably more important to manage their pain via a multimodal and multidisciplinary approach than other patients in the hospital, as they often have some level of organ dysfunc-

tion as well as cognitive and sensory deficits. These patients are also more likely to have adverse effects and drug interactions due to polypharmacy than younger patients with fewer comorbidities; therefore, adding as few new medications as possible is preferred.

As we age, we develop physiologic changes that result in the alteration of pain perception and have pharmacokinetic consequences. In the elderly, pain may not serve as a reliable warning sign of tissue damage due to alterations in various thresholds of pain based on the type, duration, and location of the stimulus. These patients experience less pain with mechanical pressure and ischemia, but experience increased pain with heat stimuli at shorter durations [14]. Their pain may present in an "atypical" manner due to the above neurologic changes as well as their alteration in pain perception. Age-related physiologic changes include low serum albumin and low muscle mass, which can lead to higher accumulation and longer half-lives of fat-soluble drugs; decreased hepatic blood flow, which decreases first-pass metabolism of some drugs; and a decreased number of functional glomeruli, which increases susceptibility to acute kidney injury and decreases excretion.

When assessing pain in the elderly with dementia, there are additional issues to consider in developing a treatment plan. Before interviewing the patient, it is important to first assess his or her cognitive abilities (using tools such as the MMSE) and to consider several normal neurologic changes such as aging brain tissue (i.e., decreased frontal gray matter loss and decline in episodic memory), visual decline, hearing loss, as well as the degree of his or her pathologic procedural and semantic memory loss due to dementia. When obtaining a history, it is a good idea to involve the patient's POA and family members and ensure that the patient has appropriate assistive devices such as hearing aids and glasses. Assessment for other modifiable factors that can exacerbate pain such as poor sleep quality, smoking, bowel/bladder incontinence, and depression should be performed and these factors should be independently treated accordingly. The VAS and/or a 21-point box scale are tools that can be used to assess pain if the patient has mild to moderate dementia. The PACSLAC or Doloplus-2 are tools that can be used to assess patients with severe dementia. Diagnostic imaging and ancillary tests should only be considered based on indications from a thorough history and physical examination, and should be pursued only if their findings are likely to change their pain management plan.

15.7 Management of Pain in the Inpatient Setting

When creating an individualized treatment plan for elderly patients with dementia, clinicians should involve the patient's family and especially their healthcare power of attorney, depending upon the patient's cognitive abilities. The degree of the patient's cognitive impairment also plays a role in helping formulate a treatment plan, and coordination with and education of the patient's family and healthcare POA may be necessary. Sound evidence-based data and reasoning should be provided and explained to the POA, patient, and involved family members and/or caregivers. The treatment plan should also be discussed with the entire multidisciplinary treatment team.

Factors including sleep, nutrition, social issues, comorbidities and depression must be evaluated and adequately addressed. Elderly patients with dementia should also undergo a thorough evaluation of their environment, with every effort made to decrease their overall stress and provide familiar cues. Their assistive devices such as glasses and hearing aids should be provided when possible.

Clinicians should always consider nonpharmacological treatments such as assistive devices, PT, OT, psychology, and music therapy. Physical and occupational therapists, psychologists, case-managers/social workers, and chaplains/spiritual advisers can potentially assist in assessing sources, related biopsychosocial issues, and exacerbating factors of patients' pain, allowing clinicians to better formulate a comprehensive treatment plan.

When starting new medications, one should carefully weigh the risks versus benefits—while this is true in any population, it is especially true in the elderly with dementia as they often have organ dysfunction, normal and abnormal physiologic and neuronal changes, and they are at high risk for polypharmacy. Also, it is most prudent to start medications at a lower dose and slowly increase them over time, as indicated and as tolerated, perhaps with the advice of inpatient pharmacists. Mild to moderate pain should be treated with NSAIDs and acetaminophen (if no contraindications) and topical medications as first-line medications. Localized pain can be effectively treated with topical preparations such as lidocaine, NSAIDs, or capsaicin. Adjuvant SNRIs, sodium channel blockers/anticonvulsants and muscle relaxants can be considered. For moderate to severe pain in the hospital, short term opioid treatment may be necessary. However, elderly patients' physiological changes of aging as well as their individual organ impairments should be considered when choosing pharmacologic treatment options.

Advanced pain treatments may be available, such as PCAs, IV infusions, and interventional procedures. Among these advanced options, PNBs should be strongly considered in the elderly in the pre/postoperative setting or in cases of acute/chronic pain control that is within a single nerve or plexus distribution, because the medication deposited acts locally, minimizes opioid intake, reduces post-op nausea/vomiting, and often results in a shorter hospital stay. All of these options should be decided upon on a case-by-case basis, as the patient's cognitive impairment may be a barrier to safely and effectively implementing these modalities. PCAs and IV infusions may not be ideal in older adult patients with severe dementia, as they carry risks for potential inappropriate use and their inability to understand and participate in care may limit the ability to safely provide these treatment modalities.

15.8 Discharge Plan for Pain Management

It is important to use rubrics such as the World Health Organization pain ladder approach to achieve pain relief, even in the inpatient setting. Medications with the fewest adverse effects and at the lowest doses possible should be recommended for the patient's homegoing use. Clinicians should exhaust topical options and

non-narcotics prior to thinking about prescribing narcotic medications for outpatient use. If the patient was using a PCA in the hospital, it must be discontinued before discharge, and an oral opioids trial should be started in the hospital, if indicated and appropriate. If needed, a consult to the inpatient pain service (if available) can be placed to obtain recommendations for doses of pain medications, including opioids, during the hospital stay and for discharge planning.

It is highly recommended to assess the cognitive ability of elderly patients with dementia and their ability to take medications in an appropriate manner at home before discharge. If patient is unable to do so, it is important to find a safer way to administer medications, such as setting alarms for certain medications and/or assigning a caregiver to provide medication on time at home. In the case of patients with dementia, inpatient pharmacists can be an invaluable resource in providing education to family members and the patient regarding pain medication, doses, and timing of medications upon discharge. Before discharge, clinicians should ensure that the patient has adequate outpatient PT, OT and other movement-based modalities arranged and scheduled if they are deemed necessary. It is good practice to reassess these needs as well as the potentially decreasing need for pain medications in the outpatient setting, and titrating medications as clinically indicated. Close follow up after hospitalization is advised, either with the patient's primary care provider or a pain specialist, if necessary.

15.9 Summary

- Chronic pain is common in the general elderly population, and is likely to be present in an elderly patient with dementia who is hospitalized.
- Pain is not necessarily a part of the normal aging process, contrary to beliefs among the public and even within the medical community.
- The elderly with dementia have a higher rate of undertreated pain.
- Aging-related physiologic abnormalities, including an increase in pain threshold for mechanical and ischemic pain, a decrease in pain tolerance, and altered pharmacokinetics and pharmacodynamics augment the risk of side effects from pharmacologic treatment.
- Pain assessment in patients with dementia ideally starts with an assessment of the degree of dementia and impairment present. Self-reported scales such as the Visual Analog Scale (VAS) may be appropriate for verbal patients with mild to moderate dementia.
- For pain assessment of nonverbal individuals, behavioral observation scales such as the Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC) or Doloplus-2 are recommended.
- This population is more likely to have multiple comorbidities (and associated polypharmacy), some level of organ dysfunction due to age, and cognitive dysfunction from their dementia, which can make treatment planning and especially pharmacologic management more difficult.

- The management of chronic pain in older adults is best accomplished through a multimodal approach, including physical rehabilitation, psychological therapies, music therapy, and the involvement of social workers/case managers as well as their healthcare POA and family members.
- Conservative, non-pharmacological management is the first line treatment of choice for pain. These could consist of, but are not limited to, PT, OT, music therapy, assistive devices, orthoses, psychological support, and treating insomnia, depression and other comorbidities.
- Pharmacologic management should be based on evidence-based data from the updated 2019 Beers Criteria, ASA guidelines, and other clinical society guidelines.
- More invasive techniques such as IV infusions, PCA pumps, and interventional procedures can be considered after exhausting conservative measures.
- Improving the quality of life, optimizing functional independence, and minimizing disability in older adults should be the goal of all treatments.

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Chapter 16
Acute Pain in the Chronic Pain Patient

Eric Reilly, Larry Manders, and Keth Pride

16.1 Introduction

Pain itself is a complex neurological process that involves numerous signals and receptors between the peripheral and central nervous systems. It is often categorized as acute, generally lasting less than 3 months, or chronic, lasting more than 3 months.

Patients subject to both acute and chronic pain can be treated with a wide array of medicines and techniques, including opioids. Opioids have strong effects to prevent pain via binding to and altering opioid receptors in the nervous system. While this can be very effective for acute pain, it poses a dilemma for chronic pain as opioid receptors are subject to internalization, desensitization, and downregulation as a result of chronic opioid exposure [1]. For chronic pain, a patient may require regular opioid dose elevations or opioid rotations to achieve an equivalent amount of pain relief over time. If you compound the aforementioned scenario with an instance of acute pain, providers face the challenges of maintaining both adequate

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Eric Reilly and Larry Manders developed the intellectual properties, literature search, and composition of manuscript.
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analgesia and safety in a patient where the most potent pain medications available provide sub-optimal effects. Thus, a patient with chronic pain receiving chronic opioid therapy requires a unique approach to effectively manage any acute or worsening chronic pain.

16.2 Risk Factors

When considering the inpatient treatment of moderate to severe acute on chronic pain, opioids are often the first drugs considered. Although opioids are usually effective at treating cases of acute pain, most patients consulted for pain management are often already on some form of chronic opioid therapy. Therefore, a natural thought would be to simply add more opioids into the equation. However, this is not practical or safe without precautionary steps, as opioids have numerous possible side effects including nausea, emesis, respiratory suppression, bradycardia, and even death. Thus, in an effort to limit risks, patients are often subject to oligoanalgesia, defined as the inadequate prescribing of analgesics for individuals experiencing pain [2, 3]. Individuals at the extremes of age are also at risk for oligoanalgesia, secondary to communication barriers and increased concerns for adverse effects [4, 5]. Unfortunately, and to the dismay of medical stewardship, socioeconomic and racial differences have also been correlated with the undertreatment of both acute and chronic pain [5, 6]. In many instances, the failure to provide appropriate analgesia is likely related to insufficient knowledge in either nursing staff, prescribing providers, or both [6].

16.3 Diagnosis

A patient's pain may be assessed via a wide variety of pain scales including but not limited to a visual analogue scale, verbal rating scale, or numerical rating scale. It is important to determine the severity of any acute pain as well as chronic pain, therefore a detailed history and physical must be performed [7]. Once the etiology and details of the acute pain source have been identified, they should be evaluated and compared in context with any previous chronic pain conditions from which the patient might also be suffering. If the patient is already using opioids for chronic pain, then the current daily opioid use and morphine equivalent daily dose (MEDD) should be assessed so that a baseline treatment regimen may be determined. It is important to recognize that a patient's chronic treatment regimen may be inadequate for treating acute on chronic pain. Alterations and dose escalations are often necessary and appropriate if accompanied by a plan for eventual de-escalation.

Any adjunct treatments, in addition to the patient's baseline, depend upon the patient's level of pain and a prognosis for acute pain resolution. When assessing acute pain in a patient undergoing chronic opioid therapy the indications and meth-

ods for specific treatment plans are often subject to additional research and expert discretion [8]. However, as a means of creating a treatment plan with the patient, there are three general prognoses to consider:

- Prognosis 1: An acute episode of pain, such as cholecystitis, which should resolve in a few days with appropriate intervention. This scenario often merits the use of short-acting analgesic therapies for a few days of pain control, in addition to an unchanged chronic analgesic regimen.
- Prognosis 2: An acute episode of pain which is attributed to something more severe and slow healing, such as a pelvic fracture. This scenario often requires days to weeks of additional short-acting analgesics for breakthrough pain and may even require additional long-acting analgesics to meet the patient's increased chronic pain needs.
- Prognosis 3: An acute episode of pain which will likely become chronic and add to a chronic pain burden, such as cancer-related metastasis. This scenario often requires-short acting analgesics as well as *additional* long-acting analgesics and may even indefinitely elevate the patient's baseline chronic pain medication needs.

After categorizing a patient's pain prognosis, it is important to define their analgesic needs—specifically their opioid requirements. Considering the potential negative effects of opioid withdrawal or overdose, it is important to keep patients within a relative window of any existing opioid therapy. Due to varying doses and strengths of different opioid formulations, it is wise to define a patient's opioid needs by a single value. A useful way to do this is by converting opioids to a common unit such as a morphine equivalent daily dose (MEDD) via an opioid equianalgesic dosing table (Table 16.1). Multiple dosing tables or calculators are available online and are updated regularly, however the accuracy and recommendations of such tables are inconsistent. Providers should exercise caution and preferably 'under-dose' when utilizing such conversion tables for purposes of opioid rotation or titration [8].

Table 16.1 Opioid conversion table

Opioid	Route	Dose (milligrams [mg])	Conversion factor	Oral morphine equivalent (OME)
Morphine	Oral	15	1	15
	Parenteral	5	3	15
Codeine	Oral	100	0.15	15
	Parenteral	60	0.25	15
Fentanyl	IV	0.1	150	15
Hydrocodone	Oral	10	1.5	15
Hydromorphone	Oral	4	3.75	15
	Parenteral	1.5	10	15
Oxycodone	Oral	10	1.5	15
Oxymorphone	Oral	5	3	15
	Parenteral	1	15	15
Tramadol [2, 9]	Oral	67.5	0.22222	15

As an example, consider a hypothetical patient who receives chronic opioid therapy consisting of 200 mg of long-acting oral morphine daily and 20 mg of oral hydrocodone three times a day for breakthrough pain. This patient's morphine MEDD is 200 (200 mg × 1 per day × 1 conversion factor) and their hydrocodone MEDD is 90 (20 mg × 3 times per day × 1.5 conversion factor). Thus, their total MEDD is 290. This calculated equivalency may then be used to help promote safe and adequate analgesia when prescribing new opioids, performing opioid titration, or employing opioid rotation.

All patients, whether opioid-naive or opioid-tolerant, are subject to the risks of opioid therapy, including respiratory depression and cardiac arrest. In an inpatient setting, risks of adverse outcomes are minimized due to routine monitoring and readily available medical supplies, but precautions are still warranted. It is recommended to utilize multiple tools, such as pain scales and calculated morphine equivalents, to accurately assess patients before initiating additional or altering existing opioid therapies. The degree of pain, chronicity of pain, response to analgesics, potential for complications, and current analgesic regimen must be established in a timely fashion. Once the aforementioned information has been analyzed, efforts can be made to best safely and correctly dose patients for treatment as described in the following sections.

16.4 Treatment

As a general rule, the best approach for both acute and chronic pain is by using multimodal analgesia. Multimodal analgesia is the practice of using more than one modality for dealing with pain in an effort to reduce both pain burden and medication side effects. Modalities may include both non-pharmacological and pharmacological management. Such inpatient practices have been shown to promote earlier oral intake, earlier hospital discharge, and earlier involvement in activities such as physical therapy [10].

16.5 Non-pharmacological Management

Non-pharmacologic strategies should be the first step in *any* episode of pain, as they have limited to no side-effects, as opposed to pharmacologic approaches. While such interventions are often less practical in an inpatient setting where patients are already receiving opioid therapies, they should still remain a primary consideration. Temperature-based therapies, such as hot or cold packs, are readily available and well-received methods of pain control due to their ability to provide both comfort and distraction. Massage, music therapy, meditation, and breathing exercises are also effective and readily accessible treatments. Special consideration should be given to acute on chronic pain patients suffering from stress, anxiety, or depression, as they are subject to amplified pain through processes of catastrophizing and pain interference. For such patients, psycho-social interventions such as patient educa-

tion and proper psychological treatment, are important modalities to consider for proper pain control [11]. Physical and occupational therapy are also vital components of pain management, as musculoskeletal stretching, strengthening, and stabilization can help to promote states of pain-free ambulation.

16.6 Pharmacological Management

Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are excellent first-line treatments for acute pain. Careful consideration of a patient's comorbidities such as decreased renal function and coagulopathy should be assessed before the utilization of other non-steroidal such as ketorolac or ibuprofen. NSAIDS and acetaminophen are extremely helpful as adjunct treatments alongside opioids, so much so that acetaminophen and hydrocodone are found together in the frequently prescribed drug Norco [12, 13].

In treating acute pain, opioids work by mimicking the molecular structures of endogenous chemicals that regulate pain in the human body. Opioids bind to receptors in the central nervous system to disrupt the flow of neurotransmitters, ultimately blocking or lessening sensations of pain. Opioids are available in a variety of fast-onset (short-acting), slow-onset (long-acting), IV, PO, and transdermal formulations to best combat both acute and chronic pain. Many patients warranting an inpatient pain consult will present with a daily long-acting opioid therapy regimen, with or without short-acting opioids for additional or breakthrough pain. Common opioid medications include tramadol, oxycodone, morphine, and fentanyl. Opioid receptors are found throughout the body, which results in a wide array of side effects when activated. Opioids can cause nausea, vomiting, constipation, drowsiness, dizziness, infertility, and respiratory depression. A major risk of opioid therapy is accidental overdose, for which treatment with the opioid antagonist naloxone is warranted. Long-term opioid use is associated with tolerance, dependence, addiction, and hyperalgesia, which can make treatment of acute pain in patients on chronic opioid regimens exceedingly difficult. One should consider the three following techniques when prescribing any opioid for individuals with chronic pain: opioid rotation, dose escalation, or addition of adjunct/long-acting opioid(s).

Furthermore, in treating acute on chronic pain in a multimodal fashion there is perceived benefit in utilizing different medications with multiple mechanisms of actions. Mixed-acting analgesics are first-line treatments for neuropathic pain and are popular choices for acute, chronic, and non-specific pain. This is in part due to their intrinsic multi-modal mechanism of pain relief. Tramadol, for example, binds to opioid receptors and also prevents reuptake of noradrenaline and serotonin, which accounts for its analgesic properties. Tramadol does not have any major organ toxicity and some studies have shown that it has less severe side effect profiles than NSAIDs or opioids [14].

In addition to multi-mechanistic opioids, N-methyl-D-Aspartate (NMDA) receptor antagonists, such as ketamine, reduce post-operative pain scores, reduce opioid requirements, and may even help treat refractory cancer pain [15]. For emergency room patients in particular, receiving 1 mg/kg of ketamine in

conjunction with an IV opioid has shown to significantly lower mean pain [16]. However, specific data is lacking in terms of ketamine dosage preparations for treating chronic non-cancer pain [15].

Like ketamine, IV lidocaine is commonly prescribed for pain control in perioperative settings to help reduce opioid use, and thus it may serve a role in treating acute on chronic pain in post-surgical patients. Utilization of IV lidocaine in post-surgical patients has been shown to successfully treat acute post-surgical pain, reduce length of hospital stay, reduce postoperative nausea, and reduce postoperative opioid requirements [17].

Although less often utilized, anticonvulsants and corticosteroids may also have a role in treating inpatient acute on chronic pain. Anticonvulsants such as carbamazepine, gabapentin, and pregabalin all are well-established in treating neuropathic pain and have also been used to help prevent chronic pain in those undergoing surgical procedures [18]. Corticosteroids can also be a useful option for treating certain types of acute pain, but, due to their robust side effect profile, they are not widely recommended for the treatment of chronic pain and should be used with caution [19].

16.7 Interventions

Patient-controlled analgesia (PCA) techniques utilize a pump which allows a patient to administer their own small doses of parenteral analgesics. It is a great tool for perioperative and emergency room pain control as it bypasses dilemmas of delay with PRN analgesic dosing and also gives the patient more control over their pain management. Studies have shown that patients report better pain control with PCA techniques rather than PRN medication administration. The drawback of PCA techniques are that they require a patient to be alert, oriented, and educated enough to effectively self-administer their analgesics [20].

Regional anesthesia techniques are diverse and provide many suitable options for both acute and chronic pain relief. They are a luxury for inpatient pain control as they require several safety precautions and skilled experts for safe administration. Examples of such techniques are single or continuous epidural injections, single or continuous intrathecal (spinal) injections, and local anesthetic nerve blocks. These modalities are commonly used peri-operatively for acute pain and have rapid onset of action, however they can also be adjusted and utilized for more chronic pain conditions, such as cancer pain, trigger points, neuralgias, peripheral vascular disease, and postamputation pain [20].

16.8 Inpatient Pain Assessment Tools

Pain is solely subjective. Thus, a patient's description of their pain must be fully appreciated during an assessment. Useful tools for assessing pain include pain scales, physiologic signs, patient responses to therapeutic interventions, and timely

Table 16.2 Pain assessment tools

Age	Assessment tool	Descriptions
Neonate	CRIES	Cry, O_2 requirement, increase V/S, expression, sleeplessness
Infant	PIPP	Observation of behavior/vitals
<3 years	FLACC	Face/Leg/Activity/Cry/Consolability
<8 years	FACES	Smile versus sad faces
>8 years	Number Rating Scale	0–10

Adapted from Hawker [21]

reassessment of pain levels. In addition, electronic vital monitoring is very useful as abnormalities such as tachycardia, tachypnea, and hypertension can indicate physiological responses to pain. Such assessment tools work best when evaluated as a whole, as there is no single best way of measuring pain. When using pain assessment tools, we recommend the following modalities based on age range (Table 16.2).

16.9 Challenges in Management of Pain While in the Hospital

Due to the subjective nature of pain assessments, physicians struggle to precisely comprehend levels of pain and degrees of pain tolerance from one patient to another. Studies have shown that some physicians may lack confidence in prescribing certain medications, such as strong opioids, for patients suffering with chronic pain [22]. This may suggest that more education on acute and chronic pain management strategies is warranted for providers of all specialties. The major challenge in managing chronic pain, as well as acute pain in patients undergoing chronic opioid therapy, is the lack of clear guidelines for assessment and management. Varied study results leave physicians with non-linear evidence of how to effectively and safely treat complicated scenarios of acute and chronic pain [22]. Despite a lack of concrete evidence there are still recommendations to safely and best treat the many modalities of acute and chronic pain [20]. We recommend a multidisciplinary approach, as outlined in the following section, which utilizes a combination of treatments to achieve adequate analgesia.

16.10 Management of Pain in the Inpatient Setting

As discussed earlier, it is important to first obtain a comprehensive history in order to correctly define the chronicity of the pain, type of pain, previous treatment interventions, previous diagnoses, drug allergies, and a history of any medication or drug abuse.

In the presence of any pain it is imperative to utilize a multimodal analgesic approach, which should start by optimizing non-pharmacologic therapies. If conservative measures are unsuccessful or are inappropriate given the situation, then pharmacological analgesics should be added in a stepwise fashion [20].

For an acute episode of pain, treating the cause, and not the symptoms, should be prioritized. For example, a patient with a ruptured appendix requires surgery, and getting the patient to the operating room should be the main priority. Once a means of treating the cause of pain has been identified, management of the pain can be more appropriately handled. Sometimes, as can be true with some chronic pain, there is no immediate determinable cause and thus, the pain must still be treated appropriately.

For acute pain management in the opioid-naïve patient, a non-opioid multimodal approach should first be considered with NSAIDs, acetaminophen, and anticonvulsants such as gabapentin. If appropriate, interventions such as regional anesthesia techniques can be considered, as well as corticosteroids, alpha-2 agonists, and NMDA receptor antagonists. A scheduled regimen of NSAIDs or acetaminophen should be administered for routine pain control [23]. If pain cannot be controlled with non-opioid therapies, then the benefits and risks of starting an opioid therapy should be discussed with the patient. If a plan is agreed upon, then the patient may be started on opioid therapy with the goal of discontinuing the opioid therapy as soon as possible, accounting for the degree of pain and patient safety [20].

If a patient is admitted to the hospital with non-opioid dependent chronic pain, first inquire about their home analgesic use. Once the patient's home dose has been confirmed with the prescribing provider, it is advisable to continue the same dose. This is appropriate to both treat the patient's chronic pain and help prevent adverse effects of potential withdrawal or overdose [24]. If the patient complains of additional pain despite treatment with their home medications, then the complaint should be regarded as an episode of new or acute pain and appropriate treatment should be initiated with a multimodal analgesic approach as previously described [20].

For the opioid-tolerant patient experiencing acute on chronic pain, there are no strict research-supported guidelines for management. The following generalized approach should be subject to expert opinion and interpreted with caution. For compounding acute pain, all options and considerations of non-opioid therapy should be utilized. If opioids are deemed necessary to treat an acute pain episode, the benefits and risks should be discussed with the patient when formulating a plan [20]. An opioid dose conversion table should be used to help determine the patient's current baseline opioid dependency via their MEDD. Once an MEDD is established, additional short acting opioids may be added in a stepwise fashion.

Research suggests that an exact threshold for safe opioid use has not been identified but most experts agree that increasing dosages to 50 or more MME per day increases overdose risks without adding meaningful pain control. Most patients requiring an inpatient pain consult are well above the 50 MME/day threshold, and

thus require routine reassessment when prescribing additional opioids. Clinicians should utilize the lowest effective dosage to minimize risks [25]. If possible, preference may be given to titrating up the patient's home dose of short-acting opioids, as therapy with an existing drug helps prevent potential side effects of a new opioid formulation [8]. When adding short acting opioids to a chronic regimen, it is generally acceptable to start with a dose that is 10–20% of the previous day's total daily dose [26]. A provider should use their personal discretion when timing successive doses and reassess the patient often. Based on known onsets of action, allow for at least 60 min between oral doses and 30 min between IV doses of short-acting opioids [26]. If attempting opioid rotation using a table-derived dose, it is generally acceptable to start at 30–50% of the calculated equianalgesic dose for the new opioid, in order to account for incomplete cross-tolerance [2]. New opioid therapies should preferentially be oral or transdermal, with a fixed-dose regimen. Opioid medications may be carefully titrated at the physician's discretion with timely follow-up to help determine pain control and monitor for side effects. If the patient's daily opioid requirement must be increased to achieve effective acute pain control, a plan should be discussed to return that patient to their baseline opioid needs after the resolution of the acute pain episode [27, 28]. The ultimate goal, as always, should be patient safety.

16.11 Safe/Unsafe Modalities

In general, each treatment modality has its own unique set of risks and benefits. The risks are commonly correlated to possible side effects from the associated medication or intervention. A detailed explanation of side effect profiles of all analgesic modalities addressed in the chapter is out of the scope of this discussion. However, it is important to note that an acute or chronic pain patient admitted to a hospital has access to a wide array of medical resources, as well as a medically supervised environment for careful monitoring. This grants inpatient arenas the ability to aggressively titrate medications, perform interventions, and rapidly assess treatment responses. Altogether, such a setting permits an increased experience in creating a functional analgesic plan.

16.12 Discharge Plan for Pain Management

- Attempt to alleviate or reduce the patient's acute on chronic pain
- If the patient's analgesic regimen increases during admission, develop a plan for reducing medications, especially opioids, to their prior baseline.
- Coordinate close outpatient follow-up in order to assess ongoing pain and help prevent conversion from acute to chronic pain.

16.13 Summary

- Obtain a thorough patient history with a particular focus on the patient's chronic pain, comorbidities, and previously attempted therapeutic approaches.
- Utilize pain scales and tools in order to track progress and attempt to provide objective assessments of both current pain and treatment response.
- Create a multimodal analgesic plan which may utilize non-pharmacologic, pharmacologic, psychologic, and regional-based interventions.
- For the opioid-tolerant patient experiencing acute on chronic pain, the following steps of management are based on the authors' expert opinions and the available, yet limited, research:
  - Assess the patient's level of pain and determine an acceptable level of pain control.
  - Calculate the patient's MEDD.
  - Continue the patient's chronic opioid dose according to their MEDD, with preference given to oral routes and existing home opioid formulations.
  - Once therapy is initiated, reassess the patient's pain and observe for any signs of adverse effects or overdose, such as decreased respiratory rate.
  - If adverse effects develop, re-evaluate the patient and discuss alternative options.
  - If pain remains uncontrolled and there are no signs of adverse effects, begin slowly adding short-acting opioids. A generally acceptable short-acting opioid dose is typically 10–20% of the previous day's total daily opioid dose.
  - Reassess the patient regularly after each additional opioid dose and allow for acceptable durations between doses. Oral doses should be at least an hour apart and IV doses should be at least a half hour apart, with preference given to longer durations between successive doses.
  - Continue this pattern until acceptable analgesia is reached.
  - The provider may also utilize methods of opioid rotation, preferentially starting at 30–50% of the calculated equianalgesic dose for any new opioid.

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Chapter 17
Pain Management in Dysphagia Patient

Hemant Kalia, Neha Pawar, and Alaa Abd-Elsayed

17.1 Introduction

Dysphagia is defines as difficulty with swallowing—it refers to problems with the transit of food or liquid from the mouth through the esophagus. Severe dysphagia can compromise nutrition, cause aspiration, and reduce quality of life. Patients who are admitted to the hospital and struggling with dysphagia pose another layer of complexity in devising a comprehensive pain management plan. The choice of medications can also be sometimes obviated due to underlying pathophysiology of dysphagia. Some of the centrally acting medications like opioids, muscle relaxants etc. should be used judiciously in central etiologies of dysphagia i.e. cerebrovascular accident, traumatic brain injury, delirium, dementia etc. [1].

Dysphagia can be attributed to multiple etiologies ranging from structural, neurogenic to myogenic in origin. Patients born with abnormalities like cleft palate or other similar abnormalities affecting mechanism of swallowing can lead to structural causes of dysphagia (Fig. 17.1).

Patients with central disorders like cerebral palsy, Parkinson's disease, cerebrovascular accident and traumatic brain injury me if he can or affect the coordination of swallowing muscles are limited sensation in the mouth and throat (Fig. 17.1).

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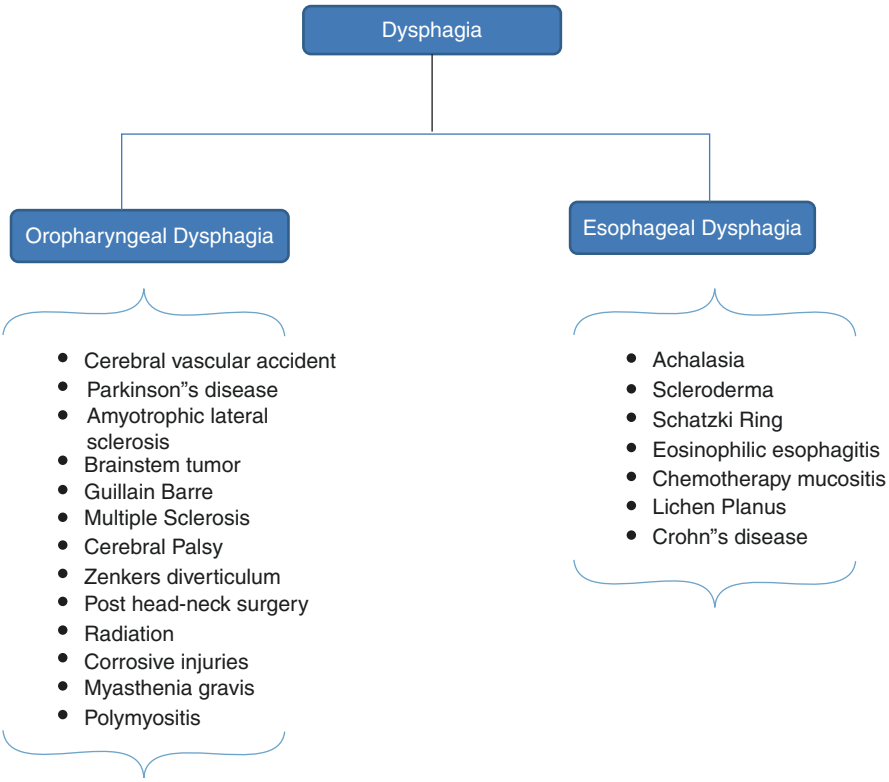

Fig. 17.1 Approach to the patient with dysphagia/diagnosis

In addition, cancer of head, neck or esophagus or even cancer treatments in these regions may cause swallowing problems leading to cancer related dysphagia.

17.1.1 Challenges in Management of Pain While in the Hospital

The main challenge is the inability to use oral medications which requires using medications that can be administered only through other routes.

17.1.2 Management of Pain in the Inpatient Setting

17.1.2.1 Postsurgical Pain Management

The management of acute pain problems in the hospital setting is best exemplified by the recent emphasis on the treatment of acute postoperative pain, release of the guidelines of acute pain management by the agency for health care policy and

research, Public health service, U.S. Department of Health and Human Services. The pain experienced following surgery often exceeds treatment by conventional analgesic regimens and poses special problems in certain situations [i.e., systemic opioids administered to ventilator-dependent patients may delay or preventing weaning from mechanical ventilation]. Consultation with a pain management specialist possessing expertise in managing pharmacological techniques such as continuous opioid infusions, patient controlled analgesic regimens, perispinal opioid analgesia, and continuous local anesthetic infusions may be extremely beneficial for the surgical patient. Nonpharmacological techniques such as transcutaneous electrical nerve stimulation may be helpful. Increasing use is being made of alternative and complementary medicine in the management of postsurgical pain. Such techniques might include audio recordings of music, guided imagery for distraction or relaxation, no therapy, massage therapy and acupuncture. The pain specialist should be aware of such resources that may be available locally and how which of these resources, if any, may be appropriate for a given patient.

17.1.2.2 Pain Management Treatment Plan

Education

Education is the key for any successful treatment plan. The first step is to educate patients regarding differences between acute vs chronic pain. This helps adumbrate a realistic and achievable pain management goal. In certain situations, it would be prudent to involve family members in developing pain management strategies.

Non-pharmacological Pain Management

A clinical practice guideline from the American College of physicians [ACP] states nonpharmacological interventions should be considered as a first-line options and chronic pain conditions like, chronic low back pain. As emphasized by ACP these therapies should be administered by practitioners with appropriate training [2].

Nonpharmacological treatment options play a very important role in the pain management treatment plan for patients who are suffering with dysphagia. Acupuncture has shown to be effective in multiple systemic review is with mental analysis, it was effective in reducing postsurgical pain compared to sham, 21% opioid reduction at 8 h, 23% at 24 h and 29% at 72 h with lowered incidence of opioid related side effects such as nausea, dizziness, sedation, pruritus and urinary retention [3–5]. A systemic review with metal analysis found acupuncture after total knee arthroplasty reduced pain and was associated with the delayed opioids use [6], Table 17.1.

A Cochran review of yoga for chronic nonspecific back pain found moderate evidence of yoga compared to exercise at 3 and 6 months [7]. Movement therapies especially Alexander technique (AT), tai chi and Feldenkrais share features of touch, directed exercise, strengthening and awareness of posture and muscle utilization in the treatment of pain and postural problems. Both Alexander technique (AT) and Feldenkrais have demonstrated benefit in chronic pain [8, 9].

Table 17.1 Evidence-based nonpharmacological therapies for chronic pain

1.	Acupuncture therapy
2.	Massage therapy
3.	Spinal manipulation therapy
4.	Mind-body directed therapies • Mindfulness, meditation and relaxation therapies • Biofeedback
5.	Movement therapies • Yoga • Tai chi • Alexander technique • Pilates • Feldenkrais
6.	Lifestyle behaviors, self-efficacy for therapies • Nutrition • Lifestyle modification

Pharmacological Pain Management

Alternate Routes of Delivery

Rectal: Rectal administration bypasses the first pass metabolism and results and absorption directly into the systemic circulation with greater drug bioavailability. The formulation of suppository affects the rapidity of absorption: Hydrophilic formulations result in much more rapid and efficient absorption than fatty suppositories.

Non-opioid analgesics:

- Acetamenophen

Opioid analgesics:

- Morphine

Intramuscular and Subcutaneous: The intramuscular route is popular for analgesic drug administration, but absorption can be erratic and repeat needling is often necessary. Subcutaneous administration of opioid analgesics can also be utilized in acute and subacute setting in certain specific situations.

Non-opioid analgesics:

- Ketorolac: 30–60 mg IM/IV Q4–6 h PRN. Max daily dose = 60 mg Limit <5 days

Opioid analgesics:

- Morphine: 10 mg intramuscular dose = NNT 2.9

Intravenous: This is often considered the "gold standard" because of the rapidity of onset of action associated with intravenous drug administration. For opioid analgesics, the concept of minimum effective analgesic concentration (MEAC) has been promulgated, this allows titration schedules providing close to 95% amelioration in severe painful conditions [10].

Patient controlled analgesia (PCA) is a further development of intravenous analgesic delivery. The basic variables of PCA are demand boluses, lockout interval (length of time between patient demand's), basal infusion rate and hourly or 4 hourly limit. Intravenous PCA is more effective than conventional administration of opioid analgesics with no increase in opioid related side effects.

Non-opioid analgesics

- Acetaminophen: (1) <50 kg: 12.5 mg/kg IV q4 h OR 15 mg/kg IV q6 h; not to exceed 750 mg/dose or 3.75 g/day. (2) ≥50 kg: 650 mg IV q4 h OR 1000 mg IV q6 h; not to exceed 4 g/day

Transdermal: Transdermal drug delivery allows for slow but controlled release of drug with avoidance of first pass metabolism.

Non-opioid analgesics:

- Diclofenac (Flector patch, Voltaren Gel)
- Ketoprofen (gel)

Opioid analgesics:

- Fentanyl (patch)
- Buprenorphine (Butrans patch)

Transmucosal: Buckle, sublingual and intranasal routes of administration provide direct drug entry into the systemic circulation with avoidance of the problems of pre-systemic metabolism. These routes are also unaffected by the delay in gastric emptying which can be associated with some of the patients suffering from neurological etiologies of dysphagia.

Perineural: In contrast to all of the preceding routes of drug administration, analgesic drugs may be delivered by direct neuraxial administration to the peripheral nerves. This can be done safely under ultrasound guidance using principles of regional anesthesia. Either a single bolus dose vs continuous infusion of local anesthetic (bupivacaine 0.25%/0.5%) using a catheter can be administered.

Epidural: Drug administration into the epidural space must pass through the dura and into the intra-articular space in order to reach the spinal cord. Some of the potential advantages of epidural instillation of medication are as follows:

- Reduced risk of post dural puncture headache and chronic CSF leak
- Permits greater flexibility in selection of site rostral placement may be combined with a lipophilic opioid for more segmental analgesia
  Margin of safety may be increased in the case of accidental overdose

17.1.3 Discharge Plan for Pain Management

If pain management is an issue after discharge patient should continue to use non-pharmacological modalities, medications that can be delivered by routes other than PO (as described in this chapter) and interventional pain procedures. It is very

important to monitor patient for gastrointestinal (GI) side effects (e.g. constipation) to make sure medications are not making a GI syndrome worse.

17.2 Summary

- Patients with dysphagia pose a unique challenge in devising a pain management plan in the hospital setting.
- In addition to understand the types of dysphagia; it is also important to keep in mind the basic pathophysiology behind etiological basis as the choice of pharmacological agent may vary.
- Emphasis should be given to a comprehensive interdisciplinary model of care including education, non-pharmacological treatments in conjunction with pharmacological agents.
- It is also imperative that a proper hand off is ascertained and a post discharge outpatient follow up is scheduled.

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Chapter 18
Patient with a Psychiatric Disorder

Anureet Walia, Ramsey W. Ali, and Rahul Rastogi

18.1 Introduction

Chronic pain is a significant health problem that affects nearly one-third of the adult US population [4], and roughly one-third of children worldwide [5]. It affects quality of life, sleep, work, socialization and increases mortality along with increasing health care use and costs [3]. Healthcare costs for chronic pain patients are staggering, amounting to more than $560–635 billion annually [4].

There is increasing evidence that chronic pain and psychiatric disorders are not only common comorbidities, but psychiatric disorders may modify the risk of chronic pain, as well as pain may contribute to psychiatric disorders [2, 6]. Functional imaging studies have suggested that a bidirectional relationship exists between chronic pain and mental health disorders [7]. This is applicable to clinical practice because this bidirectional relationship can suggest that there are shared neural mechanisms, which encourage the combination of pharmacological and psychological interventions to treat both conditions [7].

There is a sizeable body of literature indicating a high prevalence of hospitalized medical patients with psychiatric and behavioral health disorders [1]. The likelihood of improved symptoms, reduced length of stay, and the cost-effective expenditures for patients experiencing psychiatric and behavioral health concerns have the highest success rate when the issue(s) is addressed upon admission [1, 8]. Recent research has shown that more inpatient physicians are turning to a more comprehensive biopsychosocial model when evaluating patients in their medical and behavioral health [1].

It is important to note that psychiatric disorders and conditions remain varied. However, the literature does suggest there are some common branches of

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psychiatric disorders. These include the following: depressive disorders, substance use disorders, anxiety disorders, and psychotic disorders. Therefore, for the purpose of this chapter, these psychiatric disorders will be the emphasis. The disorders will all be covered in a similar fashion: symptoms, risk factors, assessment instruments, comorbidity with chronic pain, treatment (both non-pharmacological and pharmacological), and challenges to treatment. Lastly, a discharge plan for each of these psychiatric disorders will be discussed in further detail.

18.1.1 Depressive Disorders

Symptoms. According to the World Health Organization, depressive disorders are the most common psychiatric disorder, affecting approximately 300 million globally [9]. The underlying features for depressive disorders consistent of sad or irritable mood, loss of interest in previous activities, decreased energy or fatigue, difficulty concentrating, cognitive and somatic changes that significantly impair the individual's social, academic, occupational, or other important areas of functioning [10]. The key differentiation between these disorders are the total duration, intensity, timing, and likely etiology.

The exact cause for depressive disorders is not known, but seem to collectively include genetics, changes in neurotransmitter levels, altered neuroendocrine function, and psychosocial factors. Depressive disorders include the following: Disruptive mood dysregulation disorder, major depressive disorder, persistent depressive disorder, substance/medication-induced depressive disorder, and unspecified depressive disorder [10].

Risk factors. There are various risk factors that can contribute to depressive disorders. Genetics play an important factor in depression; a history of depression in the family increases the chances an individual will get it [11]. Another factor is brain chemistry—neurotransmitters occurring in the brain likely contribute to depression. Current research specifies that neurotransmitters undergoing changes in function and effect, and how they interact with neural circuits, can impact mood stability, and contribute to depression [12]. Other risk factors can include death or loss of a loved one, interpersonal conflict, and physical, sexual or emotional abuse. What has been studied more closely, is the risk factors that chronic pain plays in the role of depression [13].

Assessment instruments. Diagnosis is often based on a combination of patient reported history and a variation of depression assessment instruments. Some of the most common assessments used for depression include the Beck Depression Inventory (BD-II) [14], Clinically Useful Depression Outcome Scale (CUDOS), and the Patient Health Questionnaire (PHQ-9) [15].

Comorbidity with chronic pain. Individuals with depression frequently reported chronic pain. Depression is also noted to be most common among individuals with specific chronic pain, such as musculoskeletal pain, neck or back pain,

fibromyalgia. More than one out of three patients (34%) receiving opioid therapy reported depression [16].

Observational studies have demonstrated that individuals with chronic pain were also more likely to present depression in comparison to those without chronic pain. It has been well demonstrated that depression is not only a comorbidity of chronic pain, but also increases its risk. Depression in patients with chronic pain is associated with greater pain intensity, more pain persistence, and greater interference from pain including more pain behaviors observed by others [17, 18]. Patients with chronic pain completed suicide at 2–3 times the rate in the general population [19].

18.1.2 Anxiety Disorders

Symptoms. Anxiety disorders have common features of excessive fear and anxiety [10]. Fear is constituted by an emotional response to a real or perceived threat, while anxiety is anticipation of a potential threat. While there is a large family of anxiety disorders, phobias are the most commonly diagnosed treatment disorder [20]. However, this chapter will use Generalized Anxiety Disorder (GAD), the most common of the anxiety disorders, as a baseline for common symptoms. The criterion for GAD must include excessive anxiety and worry about multiple activities and difficulty controlling the worry. The criterion for GAD must also include three or more of the following symptoms: restlessness, easily fatigued, difficulty concentrating, irritability, muscle tension, and sleep disturbance [10].

Risk factors. Multiple risk factors can present for anxiety disorders. Gender has a role in anxiety disorders. Females have a higher GAD diagnosis than males, making up approximately two-thirds of the total diagnosis [10]. Rationale for higher rate of diagnosis include hormonal factors, cultural expectations, and more willing than males to visit physicians to talk about their anxiety [11, 12]. Other common risk factors include genetic factors, family dynamics, substance use (highly comorbid).

Assessment instruments. Hamilton Anxiety Rating Scale (HAM-A) [36], Generalized Anxiety Disorder Scale (GAD-7), Beck Anxiety Inventory (BAI) [13].

Comorbidity with chronic pain. Similar to depression, anxiety and chronic pain are highly comorbid [17, 18] for presence of symptoms of anxiety and anxiety disorders including GAD, panic disorder, agoraphobia and posttraumatic stress disorder (PTSD). Up to 50% of patients who suffer with chronic pain symptoms experience at least one anxiety symptom and up to 30% have an anxiety disorder [19]. Those patients experiencing greater pain severity were more likely to experience anxiety [20].

Fear-Avoidance Model of Pain. The fear avoidance model is a commonly accepted theoretical construct that describes the process for many individuals that transition from acute pain to chronic pain [21]. The foundation for this model involves emotions, cognitions, attention, and behaviors that all solidify fear-avoidant beliefs and behaviors. As the name of the model suggests, the key element is the emotion of fear, which is in direct response to negative cognitions that are highly

averse to actual or perceived pain. Fear becomes coalesced with pain itself, which leads to preoccupation and desire for avoidance of activities and movements that could potentially intensify pain symptoms [3].

18.1.3 Substance-Related Disorders

Symptoms. According to the Substance Abuse and Mental Health Services Administration [22], Substance-induced disorders are distinct from other psychiatric disorders in that all or most of the psychiatric symptoms are stem from the substance use. According the DSM-5 [10], substance-related disorders include ten separate classes of drugs: alcohol; caffeine; cannabis; hallucinogens (phencyclidine or similarly acting arylcyclohexylamines, and other hallucinogens, such as LSD); inhalants; opioids; sedatives, hypnotics, or anxiolytics; stimulants, which include amphetamine-type substances, cocaine, and other stimulants; tobacco; and other or unknown substances.

The DSM 5 lists several symptoms that constitute a substance use related disorder. Symptoms include the following: loss of control over drug/alcohol use, dedicating excessive time to obtain substances, routine cravings, relational difficulties due to drug/alcohol consumption, increased risk taking, increased tolerance, loss of interest in previous activities, withdrawal episodes, unsuccessful attempts to quit, impairment in social, occupational or school functioning [10]. The DSM 5 provides severity of substance use problem depending on number of symptoms endorsed. The following severity is as follows: mild (2–3 symptoms), moderate (4–5 symptoms), and severe (6 or more).

Risk factors. There is an increased risk for developing new substance use disorders after the onset of a chronic pain problem [22]. The risk was highest among those with a history of substance use disorder, family history of substance use disorder or psychiatric comorbidity. Patients with a known history of substance use disorders have increased prevalence of chronic pain and are at the greatest risk for stigmatization and undertreatment.

Assessment instruments. There are a variety of assessment instruments for substance-abuse and addiction screening. Some commonly used structured instruments include: Addiction Severity Index (ASI) (screening for problems and impairments that commonly accompany drug abuse and dependence); Psychiatric Research Interview for Substance and Mental Disorders (PRISM) (semi-structured diagnostic interview designed expressly for assessing comorbid psychiatric disorders in individuals who abuse substances); and Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA) (evaluates patients' functioning and lifetime experiences in seven domains: (1) medical conditions, (2) employment/support, (3) use of alcohol and drugs, (4) legal issues, (5) family history, (6) family/social relationships, and (7) psychiatric disorders) [23, 24]. All of the instruments listed have demonstrated strong reliability, validity, and have been utilized across many clinical settings by a wide array of mental health providers. Risk prediction

instruments like the Screener and Opioid Assessment for Patients with Pain (SOAPP), Opioid Risk Tool (ORT), and the Current Opioid Misuse Measure (COMM) offer valuable Guidance [25, 37].

Comorbidity with chronic pain. Prevalence of substance use disorder in patients with chronic pain ranges from 3 to 19% [26]. Substance use disorder in context of chronic pain includes loss of control in the use of medications, deteriorating function associated with its use. Another thing to keep in mind is, Pseudo-addiction that results from therapeutic dependence and current or potential undertreatment and abates with adequate analgesic therapy with functional improvement.

18.1.4 Psychotic Disorders

Symptoms. Psychotic disorders are classified by abnormalities in one or more of the following areas: delusions, hallucinations, disorganized thinking and speech, grossly disorganized abnormal behavior, and negative symptoms [10]. Delusions are rigid beliefs that are not open for change even when there is highly conflicting evidence. Common delusion themes include persecutory (individual believes harm is occurring or will occur to them); referential (belief that innocuous, non-personal events have direct and negative personal significance), grandiose (belief an individual has exceptional abilities); erotomanic (individual believes falsely that another person is in love with him or her); nihilistic (belief that a major catastrophe will occur), and somatic (preoccupation that health organ function is diseased, abnormal, or changed). Hallucinations are defined as perception-like experiences without any external stimulus [10]. They appear as that of normal perceptions and are involuntary. Hallucinations can appear in any sensory modality, although the most common is auditory (i.e. voices, whether familiar or unfamiliar). Disorganized thinking and speech are observed through an individual's speech. Common symptoms include derailment and loose associations in conversation as well as tangentiality in conversational flow. Less common is incoherence, where speech is so detrimentally impacted it becomes incomprehensible. Grossly disorganized behavior varies in appearance, from agitation [10].

Comorbidity with chronic pain. There have been a few studies to assess the prevalence of schizophrenia among chronic pain patients, but there has been some inconsistency. In one study, among 281 individuals with chronic pain, and predominantly back pain, schizoid personality disorder was present in 2% of the sample [27] and this was supported by two other studies [28]. In 2014, a systematic review concluded that both prevalence and intensity of chronic pain (e.g. headache and back pain) were lower among patients with schizophrenia when compared to patients without schizophrenia [29]. There is evidence that patients with schizophrenia present a decreased response to induced pain, and higher sensory thresholds [30]. Higher pain threshold observed in schizophrenia is poorly understood, but there is a thought suggest pain insensitivity might serve as a prodromal predictor of susceptibility for schizophrenia [31] (Fig. 18.1).

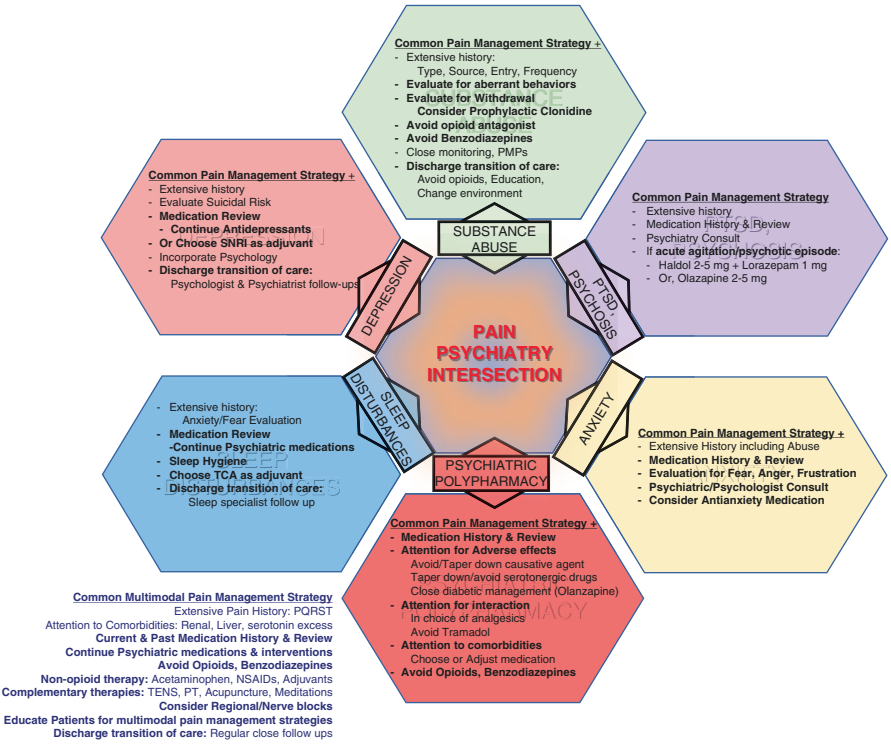

Fig. 18.1 Pain psychiatry interaction

18.2 Treatment

Managing pain in a patient with pre-existing psychiatric disorder is challenging. Patients with comorbid mental health illness have an increased risk for morbidity and mortality. This may be secondary to delay in seeking medical attention leading on to higher incidence of complications. The delay may be related to altered pain perception—increased pain perception in patients with mood disorders and decreased pain perception in patients with psychotic disorders [14]. This has a negative impact on the pain outcomes despite the increasing healthcare utilization.

In order to deal with chronic pain with comorbid psychiatric illness, we use a multimodal approach with involvement of interdisciplinary teams. The goal of multimodal treatment approach is to improve overall functioning and re-integration to normal life activities [32]. This is achieved by maximizing pain reduction, improving health related quality of life, encouraging independence and mobility, enhancing psychological well-being and preventing secondary dysfunction. It is important to use a patient centered approach and encourage self-management since patients know their pain the best.

Clinicians play a significant role by using active listening skills and demonstrating their interest in the patient's experience, thus making it comfortable for the

patient to express their pain symptoms and what they need. A thorough history of pain complaints as well as psychiatric comorbidities is warranted. Assessment instruments should be used and pain should be assessed and reassessed throughout the treatment. It is important to identify psychiatric comorbidity early on in order to provide better treatment. It is extremely important to recognize the risk of substance use disorder and suicide in patients with chronic pain.

Although patients needing acute pain management while in the hospital or emergency department, have pain as their primary focus of complaints, the decision making should involve a thorough evaluation of possible psychiatric comorbidities. A detailed evaluation is necessary and should be patient specific. A patient presenting in the emergency department with a long-standing h/o chronic pain with comorbid psychiatric disorder is different from a patient presenting with pain status post motor vehicle accident and comorbid psychiatric illness. A thorough evaluation including suicidal;/homicidal ideation, acute traumatic memories from the accident, any h/o past trauma or post-traumatic stress disorder, substance abuse/withdrawal, etc. would be needed and addressed early for better pain outcome.

Treatment generally consists of medications, psychological/behavioral interventions, physical therapy/rehabilitation, procedural interventions (nerve block, neurosurgical procedures).

18.2.1 Pharmacologic Therapies

Opioids are the primary analgesics for acute nociceptive pain. The goal should be to treat pain with the lowest effective dose of opioids. The prescription should be for a short term with clear tapering instructions at discharge (Table 18.1). Opioid analgesics

Table 18.1 Guidelines for prescribing opioids

Detailed evaluation and assessment	– Obtain a detailed history – Perform a thorough physical exam – Assess comorbidity – Assess the impact on quality of life including impact on significant others and family. – Complete diagnostic workup
Establish a diagnosis	– Identify the quality pf pain including nociceptive Vs Neuropathic
Psychosocial assessment	– Identify comorbid psychiatric illness
Assess risk for addiction	– Use screening tools to identify patients who may need further detailed assessment
Establish an overall management plan	– Identify goals of treatment – Obtain an informed consent – Short term prescription – Manage adverse effects – Consult appropriate pain, addiction or psychological, specialties when necessary
Develop an appropriate discharge plan	– Clear tapering instructions – Appropriate follow up with physician

rapidly relieve many types of acute pain and improve functionality, but their benefits when prescribed for chronic pain are questionable, summarizes the guidelines for the use of opioid in chronic pain.

Various other non-opioid medications are used to treat chronic pain. Most of these medications target peripheral and central sensitization mechanisms of pain transmission. Various non-opioid analgesics including aspirin, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDS) are the drugs of choice for management of both acute and chronic pain. Medications from the class of antidepressants and anticonvulsants are used as adjuvants. The analgesic effects of antidepressants are thought to be independent of their antidepressant effects [33]. SNRIs and TCAs are associated with faster rates of improvement in depressive symptoms and lower rates of relapse of major depressive disorder and exhibit clear analgesic effects in a number of chronic pain conditions [34]. Attention should be paid to development of new onset suicidal thoughts, hyponatremia, serotonin syndrome, hepatic/liver toxicity (Table 18.2). First and second generation anticonvulsants are approved for a variety of neuropathic pain conditions [33]. Patients should be monitored for development of new onset suicidal ideation, sedation, confusion, risk of fall, hypoglycemia and acute renal failure (Tables 18.3 and 18.4).

Table 18.2 Antidepressants with dosing, side effects and things to monitor

	Dose	Side effects	
Duloxetine	Start with 30 mg daily; usual therapeutic dose is 60 mg; max FDA recommended dose 120 mg	– Fatal in overdose – Suicidal ideation – Stevens Johnson syndrome – Serotonin syndrome – Hepatic toxicity	– Can cause withdrawal syndrome, therefore, needs to be tapered off gradually – May take 4–6 weeks to provide relief of pain symptoms – Caution with other serotonergic agents
Venlafaxine	75–225 mg daily	– Suicidal ideation – Serotonin syndrome – Hyponatremia – Hypertension – Bleeding	– Can cause withdrawal syndrome, therefore, needs to be tapered off gradually – May take 4–6 weeks to provide relief of pain symptoms – Caution with other serotonergic agents
Amitriptyline Nortriptyline	50–100 mg daily	– Suicidal ideation – Fatal in overdose – QTc prolongation – Sudden cardiac death – SIADH	– May take 4–6 weeks to provide relief of pain symptoms – Caution with other serotonergic agents – Monitor EKG – Withdrawal symptoms: cholinergic rebound

Table 18.3 Anticonvulsants with dosing, side effects and things to monitor

	Dose	Side effects	
Gabapentin	Start with 300 mg TID; gradually increase in 300 mg increments; Maximum FDA recommended dose is 3600 mg daily	– Sedation – Suicidal ideation – Dizziness – Fall risk – Renal toxicity – Hypoglycemia	– Misuse/abuse has been reported – Pain relief may take 4–6 weeks
Pregabalin	Start with 75 mg BID; gradually increase in 75 mg increments; maximum FDA recommended dose is 450–600 mg daily	– Suicidal ideation – Acute renal insufficiency – Sedation	– Pain relief may take 4–6 weeks

Table 18.4 Serotonergic agents used commonly for treatment of pain and psychiatric comorbidity

Symptoms of serotonin syndrome (HARMED)	At risk medications
– **H**yperthermia – **A**utonomic instability – **R**igidity – **M**yoclonus – **E**ncephalopathy – **D**iaphoresis	– SSRIs – SNRIs – TCAs – MAOIs – Lithium – Tramadol – Cyclobenzaprine – Methadone – Fentanyl – Triptans

18.2.2 Psychological/Behavioral Therapies

As we know, pain experience is very subjective and is shaped by previous experiences. Clinicians can help the patients adapt to the impact of mental illness and pain on their lives and develop healthy coping skills to manage pain and stress. Cognitive-Behavioral Therapy (CBT), Dialectical Behavioral Therapy (DBT) and Acceptance and Commitment Therapy (ACT) are often at the forefront of psychological intervention for comorbidity of pain-related functional disabilities and psychiatric disorders [35]. These help patients understand the Mind-Body connection—Connection between their thoughts, feelings, behaviors, body sensations to help deal with the sense of powerlessness and deal with the fear-avoidance and catastrophic thinking pattern. Teaching patients skills such as reframing, cognitive restructuring, radical acceptance, mindfulness, guided imagery, progressive muscle relaxation, pacing strategies can enhance their ability to cope with both physical and emotional symptoms. Hypnotherapy and Biofeedback are other psychological interventions used for pain treatment. Motivational Interviewing is the evidence based psychological intervention for substance use disorders.

18.2.3 Physical Therapy

Encouraging patients to take an active role in their treatment and participate in physical therapy/rehabilitation early in treatment has shown greater success. Physical therapy when performed in conjunction with medications, psychological and procedural intervention demonstrates greater participation and success.

18.2.4 Complementary and Alternative Medicine (CAM)

Complementary Alternative Medicine (CAM) modalities including aromatherapy, acupuncture, acupressure, heat/ice, vitamin/herbal supplements, yoga, music therapy, massages can provide added benefit.

18.2.5 Patient Education

Educating patients about pain in context to their specific diagnoses helps them understand their experience better and predicts responsiveness to treatment and reduction in pain score [35]. Addressing sleep difficulty and incorporating a relaxed environment with sleep hygiene practice helps significantly with pain and mood symptoms (Table 18.5).

Table 18.5 Step-wise approach to treatment

Multimodal pain management in patients with psychiatric comorbidities: a stepwise approach			
			Action
1.	Detail medical history	Pain problem Psychiatric comorbidities Substance abuse	
		Associated other comorbidities i.e. renal, liver, cardiac etc.	
2.	Evaluate	Aberrant behaviors	
		Withdrawal	Start prophylactic clonidine
		Suicidal ideation	Have a 1:1 sitter in the room; psychiatric consultation
3.	Medicinal history	Current and past medications Allergic reactions	
4.	Poly-pharmaceutical analysis	Positive impacts	Continue appropriately
		Negative impacts	Adjust doses Alter medication

Table 18.5 (continued)

5.	Pain management (avoid opioid, benzodiazepines)	General approach	Provide education of pain management strategies Acetaminophen 500 mg 4 times a day PRN
		Determine nature of pain Inflammatory/ neuropathic/ musculoskeletal	**Musculoskeletal**—Physical therapy, TENS unit, muscle relaxant—Cyclobenzaprine 5–10 mg TID PRN **Inflammatory**—NSAID i.e. Ibuprofen 800 mg TID without empty stomach **Neuropathic pain**: Localized lidocaine 5% patch 12 h on–12 h off per day; antineuropathic agents (Table 18.3); **Neuro-Muscular**—Duloxetine 30 mg once a day; For details refer to Table 18.2
		Location of pain	Employ Nerve blocks or neuraxial blocks as a priority when possible
		Associated psychiatric comorbidities	**Depression:** Choose SNRI—Duloxetine as adjuvant (Table 18.2) **Anxiety:** Add Pregabalin or SNRI as adjuvant; May use Hydroxyzine 25 mg prn **Sleep:** Employ sleep hygiene, Add TCA as adjuvant i.e. Amitriptyline 10–25 mg bedtime **Substance Abuse**: Avoid antagonists, avoid high addiction risk medications if possible i.e. opioids, Benzodiazepines, Soma etc.; **Polypharmacy interaction**: avoid addition of Serotonergic drugs; Table 18.4 **Psychosis/Anger:** Psychiatric consultation; Haldol 2–5 mg oral/IM + Lorazepam 1 mg or Olanzapine 2–5 mg oral/IM
		Associated comorbidities	**Renal:** Renal adjustment of doses **Liver:** Choose minimally liver metabolized drug
		If opioid is a choice (Table 18.1)	– Avoid in substance abuse population—if use is only for in patient – Evaluate opioid risk stratification—employ ORT, DIRE tools, PDMP, UDT – Preferably use Tramadol 50 mg Q6 hours PRN (concern for serotonergic excess) – If necessary use Hydrocodone or Morphine or Oxycodone for short term usage
6.	Transition of care	– Formulate a clear discharge plan of care – Communicate the plan in detail with patient's provider – Educate the patient and family member about plan of care – Should have follow up visit with patient's provider in 1 week – Strongly recommend to follow up with out-patient mental health care provider – If opioid as out-patient: clear expected end point discussed and documented, only a short prescription (less than 7 days) provided, should be clearly communicate the expectation of short-term usage to out-patient provider, advice close monitoring	

18.3 Challenges/Barriers to Treatment

As discussed earlier, chronic pain can have crippling effects on an individual if their pain is not well controlled. Chronic pain management in patients receiving inpatient mental health and substance abuse treatment is challenging. This is most often related to clinicians' attitudes and lack of knowledge about pain in relation to psychiatric illness and addiction disorders [36].

There are several prominent barriers to treatment in the comorbidity of psychiatric disorders and chronic pain in inpatient care. Barriers can include both personal characteristic barriers and structural barriers [37].

Clinician barriers to effective pain treatment include:

- Fear of addiction
- When the patient reports physical pain symptoms in the presence of comorbid mental illness, their pain is not taken seriously and is not optimally assessed.
- DSM lacks in appreciating the complexity of pain mechanisms and rather points towards a linear relationship between stress and pain. Therefore, creates an assumption that physical pain in someone with mental illness is not as real as someone with an identifiable physiologic cause.
- Gender has a significant impact when considering a patient's disclosure of pain symptoms. Women are perceived as being more emotional, having a lower threshold for pain and their pain is assumed to be likely psychological in origin.

Patient related barriers include:

- Patient's perception of their pain experience is also tied to their mental health diagnosis. Unlike patients with a known physiologic illness, patients with mental health diagnosis, such as depression, may not even understand whether what they are experiencing is pain and where it is coming from.
- Using unhealthy coping strategies including self-medication with prescription medications including opioids. Failing to understand the true nature of their symptoms, the patients may start self-medicating with prescription opioids for pain and/or emotional symptoms.
- Personal beliefs regarding stigma related to their mental health diagnosis, treatment and treatment providers, cultural beliefs.
- Lack of motivation
- Physical disability and lack of self esteem
- Social avoidance

Psychosocial barriers including:

- Lack of social/family support
- Loss of job or inability to work
- Financial difficulty

Structural barriers including:

- Financial factors: lack of insurance coverage and reimbursement levels
- Racial/ethnic disparities
- Limited availability of specialized services after discharge

18.4 Discharge Plan for Pain Management

Transition of care remains a big challenge in effective delivery of care. Communication among healthcare providers taking care of patient after discharge is critical for management outcome. Discharge plan should be patient specific and should have clarity on the how the management plan is being implemented and should be evaluated to adjust as per patient evaluation. It should include what to look for, appropriate medication titration schedule and how long a specific aspect of plan should be continued based upon the outcome.

- Discharging with appropriate medications and arranging for a close follow up with primary care physician after discharge
- Follow up with psychiatrist
- Establishing relationship with the nearest pain clinic
- Referral to outpatient physical therapy/rehab
- Referral to outpatient psychology
- Referral to Vocational rehabilitation
- Establishing recovery support services, such as inpatient and outpatient substance use disorder treatment, self-help groups such as Alcoholics Anonymous, Narcotics Anonymous and other stepped care models of substance abuse treatment tailored to individual patient needs.
- Referral to MAT (Medication assisted treatment) clinic if appropriate.

18.5 Summary

- Chronic pain is a significant health problem that affects nearly one-third of the adult US population and roughly one-third of children worldwide. It affects quality of life, sleep, work, socialization and increases mortality along with increasing health care use and costs.
- For the patient, pain is a major source of physical debilitation, functional limitation, emotional distress, and social disability. For the physician, it is challenging in terms of both ongoing clinical assessment and selection of appropriate management strategies.
- Chronic pain can result in increased levels of anxiety, nervousness, and depression. Such mood disturbances, in turn, can reduce pain thresholds and complicate the development of appropriate pain management approaches.

- In order, for clinicians to provide competent care to patients with pain, it is important to listen
- To the patient's subjective experience, validating the patient's emotional and physical experience and treating both concurrently is an important clinical intervention. This requires an understanding of the complex nature between chronic pain, addiction, and mental illness.
- In order to deal with chronic pain with comorbid psychiatric illness, we use a multimodal approach with involvement of interdisciplinary teams. The goal of multimodal treatment approach is to improve overall functioning and reintegration to normal life activities.
- Treatment generally consists of medications, psychological/behavioral interventions, physical therapy/rehabilitation, procedural interventions (nerve block, neurosurgical procedures).
- Practitioners should also be cognizant of current as well post discharge circumstances in choosing modalities in formulation of care plan.
- Monitor any side effects associated with medications and adjust doses as needed. Be aware of medications and their related side effects that may worsen or improve the patient psychiatric condition while treating pain.

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Chapter 19
Patient with Suicidal Ideation

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19.1 Introduction

According to the National Center for Health Statistics, in the United States, suicide has reached a 30-year high across all age groups including action and ideation. Researchers have estimated that contemplation of suicide has occurred at least once in the lifetime of 9.2% of the U.S. population [1]. According to the

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National Strategy for Suicide Prevention, suicide rates are higher in older adults compared to most other age groups. The majority of those who complete suicide have visited their primary care physician in the year before suicide [2]. An estimated 40,000 people die annually secondary to suicide in the United States, and around 800,000 die worldwide. Risk factors for suicidal behavior include substance abuse, physical abuse, chronic pain, and various psychiatric disorders such as depression and hopelessness. An outcome of completed suicide often occurs when these risk factors combine with personality traits such as aggression and impulsivity.

Suicide ideation itself and the progression from ideation to potential lethal suicide attempts are now postulated to be distinct processes with distinct explanations and predictors. A person's ability to attempt suicide and further facilitate the progression from suicidal thoughts to suicidal acts may be affected by factors associated with diminished fear of pain, injury and death, according to Klonsky et al. [3]. Evidence suggests that the capability to attempt suicide is higher in suicide attempters than suicide ideators.

As previously mentioned, chronic pain conditions are associated with an elevated risk for suicide. In this regard, governmental pressures to limit pain medications, sedatives, and adjuvant agents has led to unintended consequences of patients having increased difficulty being able to obtain their usual medications. Thus, though there is limited data in the past few years, as the government has tried to reduce incidence of drug related overdoses by limited prescriptions from healthcare professionals, this has, in part, contributed to increasing suicidal ideation and suicide related deaths. Accumulating evidence suggests that pain and hopelessness motivate suicidal desire more than other factors. The most common methods of suicide completion are hanging, self-poisoning with pesticides, and use of firearms; however, the methods used to commit the act vary according to what countries are examined. In this discussion of suicide rates or methods found in other countries, a startling statistic has emerged: 78% of all completed suicides occur in low- and middle-income countries. General risk factors include depression, anger problems, harmful habits (smoking, alcohol misuse, illicit drugs), childhood or adulthood adversities, and family history of depression/suicide. Specific pain-related factors that predicted suicide included sleep problems, poorer perceived mental health, concurrent chronic pain conditions, and more frequent episodes of intermittent pain.

Interestingly, Harvard scientists posed the question of why pain conditions might be linked to suicide risk in 2014. Drawing upon the interpersonal-psychological theory of suicide, they suggest that chronic pain may facilitate a "fearlessness about death", which they consider to be a key risk factor for the development of suicide. Chronic pain is associated with depression, hopelessness, and facilitate a desire for escape through death and erode the natural fear of dying.

The following paper will discuss suicide, chronic pain-related conditions, their physical and psychiatric comorbid conditions, and their associations with suicidal behavior.

19.2 Identifying Pain Patient with Risk of Suicide

Clinicians should be cognizant of the numerous potential stressors that can increase patient susceptibility for suicidal ideation and behavior. This is best accomplished by using a structured approach to identify these risks factors. This strategy starts with a thorough history and physical exam. Pertinent aspects for a patient's history include significant socioeconomic stressors such as financial distress, loss of employment, increased conflict with loved ones, acute worsening of preexisting psychiatric illness, decreased motivation, medication noncompliance, feeling of helplessness of hopelessness, and any other recent traumatic life events. Physical exam findings that may suggest an increased risk of suicide include hypertension, palpitations, deterioration in function or grooming, lack of appetite, and insomnia.

Patients experiencing chronic pain have a much higher likelihood of also suffering from concurrent mental illnesses compared to the general population [4]. This intimate relationship has been described as a "dual diagnosis" and can increase the propensity of potential suicidal behavior. Retrospective data has shown that approximately 90% of patients who have committed suicide have at least one documented psychiatric disorder at the time of death [5]. Interestingly, patients with documented psychiatric illness also have a much greater likelihood to have pain symptoms, suicidal ideation, and sleep problems. Patients with depression also tend to have more severe pain scores and greater functional impairment compared to patients without depression. Depression and chronic pain have a synergistic relationship in which worsening, severe, and refractory pain is associated with more severe depressive symptoms and worse outcomes. Interestingly, even chronic pain patients with well controlled depression are more likely to relapse into a major depressive episode and attempt suicide compared to patients without depression.

One of the most important tools to prevent suicide in chronic pain patients begins with early recognition of chronic pain patients at risk for depression. Depression screening for chronic pain patients is recommended to be performed at every clinic visit. There are numerous screening tests to identify depression in the general population. However, the two screening tools most appropriate for the chronic pain population include the Beck Depression Inventory (BDI) and the Profile of Mood States (POMS) [4]. The POMS is a self-reporting tool that analyses six broad categories that include tension, anxiety, depression, anger, activity levels, fatigue, and confusion or bewilderment. The BDI is also a self-reporting tool that reviews 21 different metrics over a 1-week duration to better assess the severity of depressive symptoms. These screening tools allow clinicians to have a proactive approach to addressing issues in this special patient population.

19.3 Suicide in the Inpatient Setting

Individuals at risk of suicide may use the emergency department as a place to seek help. Emergency departments are also typically involved in caring for those patients at risk for suicide such as the mentally ill, those who abuse substances, and patient

with chronic pain conditions. Interestingly, the risk of death by suicide or a suicide attempt is the highest within 30 days of discharge from an inpatient psychiatric unit or emergency department [6]. Additionally, ~70% of patients who are discharged from the emergency department after a suicide attempt do not attend their first follow-up outpatient appointment. Therefore, the emergency department should include key components to comprehensively prevent suicide in the inpatient setting. Firstly, stabilization and safety. The physician should gather information about the patient's intent, plan, and support system (or lack thereof), and the patient should not be able to leave until the physician has thoroughly assessed them. A staff member should be assigned to stay with the patient while their treatments are being planned. The safety of the patient should be the primary concern. Once the patient is considered safe, establishing the patient history is next. The physician should be calm, non-threatening and non-judgmental toward the patient. The physician should be empathetic toward the patient and listen carefully to their answers. This is also a good time to assess the patients coping mechanisms, problem solving skills, and emotional stressors. This information is imperative to creating a treatment plan that works for the individual patient. A physical exam is next, which is crucial to determine is the patient is delusional, psychotic, or impaired by substances. If the patient has attempted suicide, the physician should treat and stabilize the patient. Finally, at discharge, the patient should have a comprehensive plan that includes outpatient services and safe transitions of care, which is a program that makes it as easy as possible for patients and providers to stay in touch, including: follow up appointments; involving family and friends in the patient care plan; and developing agreements among hospitals, health care providers, and crisis centers which can foster safe transitions between patient settings. A close working relationship between the physician and the patient will encourage the patients recovery and decrease the chance for future suicide attempts.

19.4 Suicide in the Postoperative Period

Postoperative suicide risk is another important factor of discussion. Mental health issues can decrease post-surgical recovery and depression can increase the perception of postoperative pain. Therefore, mental health and the possibility of suicide risk should be considered by health care providers before and after patients present for surgery. For example, a patient anticipating surgery can experience increased anxiety which can worsen depression symptoms, and possibly lead to a risk of suicide. Patients with depression may also take longer to seek medical care, which, if the patient condition is too advanced, can decrease the effectiveness of a surgical procedure. Depression can also be inadvertently exacerbated after a surgical procedure by health care providers. For example, the patient can have a reaction to anesthesia, antibiotics, and pain medications. Therefore, health care providers should assess their patients before, during, and after a surgical procedure to note if they currently are experiencing anxiety and depression or are at risk for developing it

post-surgery. Health care providers can educate their patients regarding the length of recovery, understanding medications and side effects, provide them with a clear follow-up appointment schedule and list of numbers to call if necessary, and a list of symptoms or changes that can occur as a result of the procedure. Furthermore, involving the patients' friends and family in their recovery process can help monitor the patient's mood and feelings for risk of suicide. Friends and family can encourage the patient to follow through with the after-care plan, eating a healthy diet, and exercising, all of which can decrease stress, anxiety, depression, and risk of suicide.

19.5 Suicide Risk in Specific Chronic Conditions

19.5.1 Arthritis

Arthritis, or inflammation of one or more joints, is caused by numerous conditions, the most prevalent being osteoarthritis, rheumatoid, psoriatic, gout, and lupus related. Based on data collected from 2013 to 2015, the Centers for Disease Control estimates that 54.4 million adults in the United States (22.7%) carry a formal diagnosis of arthritis, making it one of the most common and morbid conditions [7]. Arthritis is not only one of the leading causes of disability in the US, but also worldwide, with many associated medical comorbidities including cardiovascular disease, diabetes, and obesity. Additionally, there is a psychological strain (depression, anxiety) imposed by arthritis, the combination of which leads to overall lower health-related quality of life scores and higher rates of suicidal ideation. Park et al. extracted data from 162,598 persons taking part in the 2013 Community Health Survey and found that 16.17% of males and 21.23% of females suffered from arthritis and 8.30% of male and 13.90% of females experienced suicidal ideation [8]. Suicide attempts are significantly higher with a concomitant history of sexual or physical abuse, drug or alcohol addiction, mental health disorders, and chronic pain.

19.5.2 Fibromyalgia

Fibromyalgia is a constellation of symptoms including diffuse musculoskeletal pain, tenderness, and stiffness, without a definitive inflammatory process. This condition affects roughly six million individuals in the United States. It is postulated that the pain experienced is derived from alterations in how the brain and spinal cord interpret painful and non-painful signals. These physical symptoms are often found in combination with cognitive symptomatology (difficulty in concentration, confusion), fatigue, insomnia, and various comorbid psychiatric disorders (predominantly depression, anxiety, and borderline personality disorder). Patients with fibromyalgia frequently have a negative self-perception extending not only to

their body image, but also to their perceived self-efficacy and worth. This often impacts their interpersonal relationships, ability to work, and overall quality of life. The mixture of physical pain, cognitive changes, and psychosocial issues places these patients at a significantly elevated risk of both suicidal ideation and suicide attempts. Dreyer et al. reported the risk of death from suicide was ten times higher in females with fibromyalgia as compared to the general population [9]. Risk factors for suicidal ideation or attempts include polysomatic symptoms such as fatigue (OR 1.29, 95% CI 1.25–1.32), dizziness (OR 1.25, 95% CI 1.22–1.28), and weakness (OR 1.17, 95% CI 1.15–1.19), as well as obesity (OR 1.18, 95% CI 1.10–1.27), and drug dependence (1.15, 95% CI 1.12–1.18). Psychological treatment with cognitive behavioral therapy, multimodal therapy, hypnosis, and biofeedback techniques is paramount to lowering the risk of suicide in this particularly vulnerable population.

19.5.3 Back Pain

The Global Burden of Disease studies done between 1990 and 2010 consistently show low back pain as one of the leading causes of years lived with disability. Back pain is a principal cause of limitation in activity and subsequent inability to work throughout much of the industrialized world and carries tremendous socioeconomic burden. Estimates show that as many as 80% of individuals will experience back pain at some point in their lives, with nearly 10% progressing to chronic back pain. As with other chronic pain syndromes, risk of depression and suicidal ideation is elevated. In a Finnish study, subjects reporting back pain were found to have a significantly higher risk of committing suicide within 10 years [10]. When back pain is reported in combination with other sites of somatic pain, the risk of a suicide attempt is further elevated. Park et al. showed a significant association between lifetime suicide attempts and subjects having multiple sites of somatic pain and comorbid major depression (AOR 14.78, 95% CI 10.08–21.67, $p < 0.001$) compared to those without pain or depression [11].

19.5.4 Cancer

According to the National Cancer Institute, approximately 38.4% of people will be diagnosed with cancer during their lifetimes. In 2018 alone, greater than 1.7 million new cases of cancer were diagnosed. The rate of suicide in cancer patients is double that of the general population. In a study of over 18 million cancer patients from 1973 to 2002, highest suicide rates were reported in patients with cancers of the lung and bronchus (SMR 5.74, 95% CI 5.30–6.22), stomach (SMR 4.68, 95% CI 3.81–5.70), oral cavity and pharynx (SMR 3.66, 95% CI 3.16–4.22),

and larynx (SMR 2.83, 95% C, 2.31–3.44). Suicide risk is undoubtedly further exacerbated by cancer related pain and depression. Fortunately, many treatment protocols highlight the importance of identifying these risk factors and provide emotional and psychological support as well as aggressive treatment of cancer related pain.

19.5.5 Headache

Headache is the most common reason for referral to a neurologist in the US. Fifty percent of adults experience headaches annually, with the most prevalent types being migraine, tension-type, cluster, and medication-related headaches. Several studies have reported an association between headaches and psychiatric conditions including major depressive disorder and panic disorder. Many forms of headache are recurring and debilitating, resulting in loss in personal and work productivity. Suicidal risk was determined to be elevated in 20% of individuals in a community-based study of 121 subjects with chronic daily headaches, particularly in those suffering from migraine with aura [12]. Others have reported increased pain intensity, rather than type of headache, as the ultimate risk factor, correlating a single standard deviation increase in pain score with a 79% increased risk for attempted suicide (adjusted for gender and psychiatric disorders). Treatment of headaches, first and foremost, requires an accurate diagnosis, which often times can be difficult secondary to the similarities in symptomatology and timeline. Once a diagnosis is established, a multi-modal approach to treatment is likely beneficial. Particularly for patients who suffer from chronic migraines with aura or other headaches of severe intensity, screening for suicidal ideation should be undertaken.

19.5.6 Inflammation

Certain inflammatory conditions including infection, traumatic brain injury, and autoimmune disorders have been linked to suicidal behavior. Numerous studies have reported alterations in inflammatory mediators such as interleukins (IL-2, 4, 6, 8, 13), tumor necrosis factor alpha (TNF-α), and interferon gamma (IFY-γ) in the plasma and CSF of suicide attempters, and in the post-mortem brains of suicide completers. Additionally, inflammatory cytokine elevation can trigger depression and bipolar disorders. Furthermore, traits critical to suicide completion such as aggression and impulsivity have also been found to have elevations in plasma C-reactive protein (CRP) and TNF-α. The alignment of inflammatory cytokine linked depression, suicidal ideation, and impulsivity can result in a devastating outcome.

19.5.7 Neuropathy

Neuropathic pain, often a consequence of nerve fiber injury, is common, debilitating, and difficult to treat. While chronic neuropathic pain and depression are often comorbid, an examination of data from over 4.8 million individuals from the National Death Index and treatment records from the Veterans Health Administration yielded no association with suicidality after controlling for age, gender, and Charlson Comorbidity Index. Although there is no established link between neuropathy and suicidal behavior, it is prudent to treat the neuropathic pain and any depressive symptoms via mutually beneficial pharmacologic (TCAs, SSRIs) and psychotherapeutic interventions.

19.5.8 Obesity

Obesity, defined as a Body Mass Index greater than 30, is prevalent in an estimated 40% of adults in the United States according to the CDC National Center for Health Statistics 2015–2016. Obesity puts patients at much greater risk of developing diabetes, hypertension, cardiovascular disease, stroke, cancer, chronic pain states, and osteoarthritis. Additionally, there are often psychological consequences of obesity with meta-analysis confirming a reciprocal link between obesity and depression. The National Health and Nutrition Surveys from 2005 to 2010 showed that 43% of adults with depression were obese and 55% of those reported moderate to severe depressive symptoms despite being on an antidepressant regimen. Systematic reviews predominantly show an inverse relationship between obesity and completed suicide (obese individuals are less likely to commit suicide); however, suicidal ideation and attempts were gender specific, with obese females at increased risk.

19.5.9 Substance Abuse

One of the most commonly cited risk factors for suicidal behavior includes use, abuse, or dependence of various substances, particularly alcohol, opioids, cocaine, and inhalants.

A meta-analysis of 420,732 study participants showed a significant association between alcohol use disorder and suicidal ideation (OR 1.86, 95% CI 1.38–2.35), suicide attempt (OR 3.13, 95% CI 2.45–3.81); and completed suicide (OR 2.59, 95% CI 1.95–3.23) [13]. An empirical review showed significant elevations in standardized mortality ratios (SMRs) for individuals with alcohol use disorder, but even higher SMRs for those with intravenous drug use and mixed drug use [14]. Individuals are at particularly high risk for suicidal behavior when substance use combines with risky sexual behavior or psychiatric comorbidity [15].

19.6 How to Treat a Pain Patient at Risk of Suicide

The connection between chronic pain, depression and suicide has been well established in the literature [16]. The American Psychiatric Association includes chronic pain as a risk factor for suicide completion. In their most recent practice guidelines published in 2016 they recommend all psychiatry providers evaluating suicide risk to include questions about chronic pain. The CDC estimates that 1 in 5 adults carry a diagnosis of chronic, non-malignant pain, and with this diagnosis comes a wide range of limitations in the patient's functional, social, recreational and financial lives [17]. Of these patients, the suicidal ideation rate has been found to be 20% with a lifetime prevalence of suicide attempt between 5 and 14% [16]. Completed suicide in chronic pain patients is twice that of the regular population [16]. Understanding how to approach a suicidal patient in your office is becoming a necessary part of a pain medicine training curriculum.

In order to treat, we must first recognize the high-risk suicidal patient. The interpersonal theory of suicide suggests that suicidality stems from an unfulfilled need for social connection and a feeling of being a burden to others. These are key points that should be evaluated in every pain patient. Furthermore, Fishbain et al. found a number of predictors for suicidal ideation, suicide attempt and suicide completion that should alert you to screen a patient more thoroughly. These predictors include depression, current smoking history, disability, a perception of the patient being a burden to others, a history of sexual or physical abuse, PTSD, male sex, older age, functional impairment, poor relationship with family, family history of mental disorders, aggression and psychiatric comorbidities [18]. And, of course, a history of suicide attempt is the strongest predictor of future suicide completion. This list may present warning signs that are common in the chronic pain population, and does not automatically indicate concern for suicide, but a physician needs to recognize changes in emotional stability which may warrant further screening and discussion on the topic.

Many experts recommend using screening tools to assist you in the recognition of these high risk, depressed patients at every office visit. There are numerous validated tools that can be used to inspire a conversation about mood, emotional functioning and suicidal ideation. You should consider an assessment tool that coincides with your medical practice's time, finances, ancillary staff and literacy of patient population.

When a healthcare provider encounters a patient, who presents himself as being acutely at risk for suicide, one should make an attempt to discuss the issue openly. There are several warning signs that carry the highest risk of impending suicide attempt and necessitate prompt evaluation: outwardly threatening suicide, looking for a means to kill oneself (including pill-seeking, weapon-seeking etc.), and talking or writing about death, dying or suicide. In a situation like this it may actually be easier to guide the clinic conversation toward these difficult issues. With a patient who you suspect may have suicidal ideation, but is not outwardly revealing, a good place in the interview to broach this topic is after the detailed pain assessment,

before the physical exam. If a physician has practiced talking about this topic out loud, it will be easier to execute in a high stress, emotionally charged encounter. You should know the topics to tackle beforehand and have practiced the flow of such inquiry.

All patients should be asked about previous suicide attempts, present suicidal ideation and/or future suicide plans. Patients should be questioned if they have access to firearms, other weapons or large doses of lethal medications. Occasionally, an acutely suicidal patient may deny suicidal ideation due to stigma, fear of reprisal or fear of ridicule. If a patient presents in such a manner as to alert the clinician that there is an inconsistency between his response and the truth, it is okay to acknowledge and vocalize your apprehension. Let the patient know you are concerned. An actively suicidal patient should not be left alone in your clinic. Steps should be taken to have the patient transferred to the nearest inpatient facility that can manage and treat psychiatric crises. If the patient is not actively suicidal but has made reference to suicidal ideation or suicide plan, he requires an outpatient mental health assessment as soon as possible, but may not warrant an inpatient admission. These patients mandate close and frequent monitoring. Asking about suicide does not plant the idea in your patient's head! Do not be afraid to ask.

Treating chronic pain in suicidal patients can be difficult. Oftentimes these patients exhibit greater pain catastrophizing and poorer coping skills than their non-suicidal counterparts. Dr. John Kowal examined changes in suicidal thinking following an interdisciplinary pain treatment program of 250 participants and found that this treatment modality may result in reduced suicidal thinking [19]. This study included a 3-week active treatment phase with the involvement of medicine, nursing, occupational therapy, pharmacy, physiotherapy, psychology, social work and therapeutic recreation. Participants also underwent 25 h weekly of didactic lectures on financial resources, managing headaches, sleep problems, pain medications etc. Although this approach may be prohibitively time intensive and costly, it showed a very significant decrease in suicidal thinking and should emphasize the importance of a multi-modal, interdisciplinary approach to pain treatment in this population.

Opioids are a commonly used treatment modality for acute and chronic pain disorders. Although effective, there is a clear and dose-dependent relationship between opioid use and unintentional overdose and suicide [20, 21]. There is also a clear association between opioids and other recreational drugs, central nervous system depressants—like alcohol and benzodiazepines—and overdose. For this reason, opioids have recently been the focus of multiple national campaigns to diminish or even eliminate use in chronic pain practices [22]. Their therapeutic index is too narrow and their potential to be misused too high to prescribe to patients at risk for suicide. If opioids are absolutely necessary in this patient population, the physician should attempt to prescribe the lowest possible dose with the smallest possible quantities [23]. The Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain state that opioid doses should remain below 90 morphine milligram equivalents for all patients, but especially for patients at risk for suicide [24]. Additionally, these patients should return frequently for in-office appointments and should be screened at each visit for suicide ideation. A naloxone

kit with an educational component for family members should always be prescribed to these patients as well.

Antidepressants are the universally accepted first-line treatment for depression and suicidality. There is, however, a black box warning for all antidepressants regarding a paradoxical increase for suicide after initiation in patients between 18 and 24 years of age. Moreover, elderly patients often have trouble tolerating the side effect profile of many of our more common antidepressant medication. In an acutely suicidal patient, initiating a new antidepressant may not be wise, unless you are able to closely follow the patient while titrating and adjusting the medication accordingly. Refer these patients to psychiatry colleagues early and communicate directly with their providers.

The best treatment modality for suicidal patients with chronic pain seems to be engaging the full spectrum of multi-modal pain relief. All disciplines possible—including interventional pain medicine, psychiatry, physical medicine and rehabilitation, psychology, chiropractic medicine, acupuncture, massage therapists—should evaluate and treat the patient. Opioids and other addictive medications should be avoided or used sparingly. Antidepressants, antiepileptics, NSAIDs, topical agents should all be utilized in accordance with patient's comorbidities overseen in conjunction with the primary care team and psychiatry team. An emphasis should be placed on pain control, but also on teaching coping skills, sleep etiquette, encouraging productivity and social interaction. Managing suicidal patients with chronic pain is a difficult, but crucial task that the pain physician will encounter many times throughout his practice.

19.7 Discharge Plan for Pain Management in Patients at Risk of Suicide

When discharging a patient at risk of suicide, thorough planning is essential for the patient's safety. While a healthcare provider might assume that the patient has overcome their crisis and is therefore safe, studies have shown that suicide rates immediately after discharge are three times higher than those seen during inpatient treatment, and 15 times higher than the national suicide rate in the US. In fact, one-third of all suicides committed by patients with mental disorders occur within 3 months of discharge from inpatient care. Though rates decrease greatly after this period, risk remains elevated for an entire year following discharge [25]. In light of these statistics, it is clear that outpatient follow up must be carefully planned and implemented in any patient at increased risk of suicide.

One of the most important factors in discharge planning is early contact with a medical provider. One study done in the UK found that standardized follow up of patients within 7 days resulted in a significant decrease in suicides within 3 months of discharge [26]. However, only half of psychiatric patients in the US are seen by a healthcare provider within 1 week [27]. This is concerning because 80% post-treatment suicides happen within 4 days of discharge, and 40% happen on the first

day after leaving the facility. It is possible that contact with patients within the first week could drastically reduce suicide rates. However, some experts believe that it is not sufficient to simply set an appointment. One study reviewed root cause analyses of post discharge suicides and noted that even when patients had an appointment within a week, 50% of patients died before the appointment occurred and 20% of patients cancelled or did not come to the office visit [25]. This indicates a need for immediate and regular check ins with patients, as opposed to traditional follow up appointments. Some practitioners believe that the answer to this question lies in mobile health technology such as text messaging and apps, which would allow for more immediate, frequent patient communication. Apps such as these would also make it easier for patients to contact emergency services if the need arose. However, studies have not yet been done to assess the mortality benefit of these tools.

One option when discharge planning of a patient at increased suicidal risk is the negotiation of a "no-suicide" contract. This technique is commonly utilized among outpatient psychiatrists and counselors. The contract may be written or verbal and is an agreement between a patient and a healthcare provider that the patient will not harm themselves. The patient agrees to notify family member or medical personnel when faced with overwhelming suicidal thoughts, rather than acting on those impulses. Proponents of the "no suicide" contract believe that it can be helpful in establishing a therapeutic relationship with the patient and decreasing physician anxiety. These contracts may also have diagnostic value when used in the evaluation of suicide risk. For example, patients who refuse to abide by a contract might be considered higher risk than patients who agree. These contracts have the best chance of success when used under certain parameters. Contracts should only be established with patients who are not in imminent danger. If patients are deemed to be an immediate risk to themselves, they should be hospitalized rather than followed in an outpatient setting. Contracts should only be used as short-term agreements. A contract typically states that a patient will not harm themselves for a period of 3–7 days. At the end of this period, the patient should be seen by a mental health provider for reevaluation. When used for the correct patients, many physicians believe that these contracts are useful for protecting patients and increasing personal peace of mind after discharge.

However, there are many arguments concerning the efficacy of the "no-suicide" contract despite its widespread use in psychiatric care. Though several studies have been performed to assess the effect of these agreements, researchers have failed to demonstrate any mortality benefit [28]. This is supported by statements from many mental health providers who regularly implement these agreements in their practices. For example, a poll of psychiatrists in Minnesota revealed that 41% of physicians who use contracts reported cases of attempted or completed suicide despite a standing contract [29]. Other opponents believe that the use of a contract may be detrimental. A physician may erroneously believe that a patient is not in immediate danger because he or she verbally agrees to a contract while internally planning self-harm [29]. Some oppose the contracts because they do not confer any legal protection for the physician in the event of suicide [30]. Some healthcare providers,

therefore, choose to err on the side of caution and prolong inpatient treatment rather than rely on contracts.

Unconventional methodology alongside traditional treatment plans seem to be commonplace when dealing with patients with suicidal activity because of the complexity of the disease process and intertwining of socioeconomic circumstances contributing to their illness. Complementary and alternative medicine have become popular in the US with up to 33% of the general population using these therapies and upwards of 70% of chronic pain patients using these therapies in conjunction to their normal pain regimen. Complementary and alternative medicine therapies include yoga, meditation, acupuncture and massage. For example, if an alternative therapy does provide positive results to decrease pain that are backed by scientific literature, it is a disservice to withhold that option from a chronic pain patient. Therapies that have not necessarily been proven to objectively decrease pain but have been proven to decrease the perception of pain to a patient are also options that should be offered to a patient to provide complete, comprehensive care. By offering non-traditional options for patients to try, this allows patients to have multiple options and develop an individualized and personal plan that may be more beneficial for one patient than another. This may prohibit the patient from being under the impression that they are running out of options after they have been tried on various medications at differing dosages.

Using modern pharmacologic therapy alongside cognitive behavioral therapy is the first line therapy for treatment of major depressive disorder but use of cognitive behavior therapy alone has also been proven to decrease suicidal behavior. Cognitive behavioral therapy is time intensive and requires consistent and frequent follow up from the patient. The nature of this intervention reinforces the results supporting the claim: suicidal psychiatric patients have a marked decrease in suicidal behavior given a follow up appointment within 1 week of discharge from psychiatric facility. It is vital that a physician schedule a close follow up appointment for a suicidal patient and reinforce the importance of a patient's compliance to their prescribed medication regimen and attendance of the follow up appointment. The physician is responsible for knowing the environment that the patient is being discharged to and making sure that the individuals living with the patient are aware of the patient's status and vulnerability so that they can remove any weapons from the home that they will be residing in. Gaining permission from the patient to discuss their recent hospitalization/suicidal activity with a close relative or friend can potentially be lifesaving. Having a support system in place will put accountability on more people to ensure that the patient return for follow up after discharge and adhere to the advice of their physician. Maintaining a relationship with a primary care physician to continue comprehensive care, management of medications, and regular checkups is crucial to well-being of all patients but even more so with the patients with a history of suicidal ideation. As a physician, making a conscious effort to discuss a topic as difficult as suicide with patients can make the difference between seeking treatment and carrying out a plan of suicide. Physicians have a responsibility to protect their patients and encourage them to act in their best interest even if protection from

themselves is what is in their best interest at the time of a crisis. Educating patients on the options they have in emergent situation as well as routine care is well within the scope of any physician's practice. Providing patients with these resources legitimizes their concerns and their illness which will build a trusting foundation between a physician and their patient.

19.8 Summary

- Clinicians should be cognizant of the numerous potential stressors that can increase patient susceptibility for suicidal ideation and behavior.
- Patients experiencing chronic pain have a much higher likelihood of also suffering from concurrent mental illnesses compared to the general population.
- Depression and chronic pain have a synergistic relationship in which worsening, severe, and refractory pain is associated with more severe depressive symptoms and worse outcomes.
- Furthermore, individuals at risk of suicide may use the emergency department as a place to seek help. Therefore, the emergency department should include key components to comprehensively prevent suicide in the inpatient setting.
- Finally, postoperative suicide risk is another important factor of discussion. Mental health issues can decrease post-surgical recovery and depression can increase the perception of postoperative pain.

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Chapter 20
Intubated Patient in the Intensive Care Unit (ICU)

Sarah E. Schroeder and Peggy Y. Kim

20.1 Introduction

Patients who are admitted to the critical care unit often experience pain due to multiple reasons, including their initial injuries or surgical wounds, as well as procedures unique to their high acuity care setting, such as invasive line placement, bronchoscopy and wound cares. Additionally, other less obvious causes of pain include blood draws, respiratory exercises and physical therapy sessions. The determination of patients' levels of pain in this setting has historically been difficult to quantify and thus often limits our ability to treat their pain. This leaves many patients with pain that is untreated or undertreated, which not only is distressing to patients but also increases morbidity and mortality. In patients whose pain is over-treated, this may also lead to unwanted effects such as hypoventilation, sedation, and organ dysfunction from drug side effects. Improved pain control while in the hospital has been associated with shorter length of stay, improved patient results and decreased cost of care [1]. In this chapter, we will discuss the pathophysiology of pain in critical care patients, pain assessment tools useful in the ICU setting, risk factors for the development of long-term pain and treatment options for the intubated patient in the critical care unit.

20.2 Pathophysiology

There are multiple medical issues from which patients may suffer in the critical care setting; these can vary widely depending upon the type of ICU in which they are receiving care (cardiac, trauma, neurological or medical). However, despite their

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initial reason for admission, high acuity patients often have similarities in co-morbid conditions, which may have been either pre-existing or may have developed during the admission. Unfortunately, some of these conditions may limit our options for pain control.

Delirium is universally common in the critical care setting, affecting up to 80% of patients [2]. The diagnosis as stated by the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV is a "disturbance of consciousness and cognition that develops over a short period of time (hours to days) and fluctuates over time" [3]. The altered consciousness and cognition associated with delirium can include both hyperactive and hypoactive states. Not only is this condition distressing to patients and their families, but it is also a major contributor to morbidity and mortality. The cause of this altered state is often multifactorial, but there are known contributors. Patient risk factors for the development of delirium include older age, previous cognitive impairment, depression, alcohol use, smoking, hypertension and vision or hearing impairments. Factors that arise from hospitalizations include organ dysfunction with significant metabolic disturbances, infection, hypotension, respiratory disease, prolonged immobilization, sleep disturbances and medications. In addition to increased morbidity and mortality, delirium itself is a known risk factor for other complications in the critical care setting, including inadvertent self-extubation and removal of other catheters, failed extubation, prolonged hospital stay and increased healthcare costs [2]. Furthermore, delirium may predispose patients to later cognitive impairment even after they leave the ICU, if they are able to do so [4, 5]. Although sometimes difficult, it is important that we recognize delirium when it is occurring and attempt to optimize any risk factors, if present, such as keeping the lights as low as possible in patient rooms during the evening/nighttime hours and returning eyeglasses and/or hearing aids as soon as possible.

The level of sedation used in the critical care setting has implications for the development of delirium, but also for several other aspects of patients' care. When patients are over-sedated, it reduces the likelihood that they will accurately report pain and thus may lead to under-treatment of their pain. Additionally, increased sedation may negatively affect many other issues with regards to their medical status, including prolonged ventilation, increased length of stay and increased hospital costs. Therefore, it is important to achieve the optimal level of sedation to maintain appropriate ventilation while intubated, and to treat pain as a separate issue to be addressed by other means.

When patients are intubated, the ideal amount of sedation and pain medication allows them to be able to breathe on their own with minimal ventilatory support but also be comfortable with regards to their pain control. If there is increased pain during the ventilator weaning process, it may lead to difficulty separating from the ventilator as patients will often initiate lower tidal volumes, have lower FRC and decreased cough reflexes. Additional time on the ventilator leads to additional complications including lung injury, infection, muscle atrophy, immobilization and death. Therefore, it should be our goal in intubated patients to allow them to wean

as quickly as is physiologically possible given their pathology. The treatment of their pain often plays a major role in this process.

Organ dysfunction is unfortunately all too common in critically ill patients, and thus requires the critical care physician to carefully assess the choices for sedative and pain medications in this population. Patients may have pre-existing organ dysfunction that eliminates options for pain control. Additionally, as patients' critical illnesses deteriorate, we often see cardiac, liver and kidney dysfunction. Cardiac dysfunction can also be directly due to their uncontrolled pain. Some examples include stress cardiomyopathy or myocardial injury following non-cardiac surgery (MINS) as well as asymptomatic troponin elevation due to inadequate pain control. Providers need to be cognizant of these possibilities, in order to adjust or remove medications that may have altered pharmacodynamics with any newfound dysfunction.

20.3 Risk Factors

Patients in the critical care unit often have a plethora of reasons for experiencing pain, including chronic or newly diagnosed medical conditions, nursing cares, procedures and traumatic injuries or surgical wounds. In addition to the treatment of overt pain, there are several other reasons why a patient may receive pain medications in this setting, including ventilator synchrony, sedation if intubated, and to minimize agitation. As stated above, the medications delivered are not without risks. In addition to the known pharmacodynamic effects of pain medications, practitioners also need to be aware of the increased risk of future chronic pain disorders.

It has been shown that patients who experience unrelieved acute pain in the critical care setting have an increased risk of developing chronic pain syndromes later in life. The definition of chronic pain by DSM-5 criteria indicates that pain lasting at least 3–6 months beyond the expected period of healing for a certain injury may be diagnosed as chronic pain. Researchers found that up to 44% of patients who were previously admitted to the ICU experience chronic pain that was not previously present at the 6 month mark after their hospital discharge [6]. Many of these patients experience pain after a procedure that they may have received surrounding their ICU stay; if this pain meets criteria, it may be classified as chronic postsurgical pain (CPSP). The definition of CPSP indicates that the experience of chronic postsurgical pain lasts for at least 3–6 months after surgery. Risk factors for the development of CPSP include patient factors such as female sex, younger age, preoperative pain syndrome and opioid use. Other risk factors include the specific type of surgery that the patient underwent and the treatment of their postoperative pain. Surgeries that incur the highest risk of developing CPSP include sternotomy and limb amputation. Patients that have uncontrolled and severe pain post-operatively that is not adequately treated are also at higher risk for development of CPSP. Knowing these risk factors, clinicians in the perioperative setting should aim to minimize significant pain using multimodal therapies, to be discussed below.

20.4 Diagnosis

The Society of Intensive Care Medicine (SICM) recommends that pain should be routinely monitored in all patients, with the gold standard being their self-report of pain. This assessment can be difficult in patients who are intubated, as there are many factors that are common in critically ill patients that may limit their ability to communicate, including sedation and delirium. Moreover, the endotracheal tube itself does not lend itself to easy communication, as patients are often required to write down their questions and answers or resort to using hand gestures or other behavioral expressions. However, even if patients are unable to verbally indicate their pain level, they should be given the option to express their pain on an intensity scale (0–10 or the faces scale) by pointing at a chart or writing, if their mental status permits [1]. It should be stressed that the description of both of these tools states that the scoring should be performed at regular intervals. If the patient's pain levels are not measured at regular intervals, these assessments should at a minimum be performed before and after an intervention. Repeating these assessments allow practitioners to ascertain whether or not an intervention was helpful to the patient and if not, a different therapy may be attempted for future painful episodes.

Traditionally, we have relied on objective data such as vital signs as an indication of pain, as tachycardia and hypertension are commonly associated with pain. However, hemodynamics alone are not sensitive or specific enough to truly capture the complexities of and by definition the subjective nature of pain, and may be abnormal for many other reasons unrelated to pain in critically ill patients.

In an attempt to create a standardized and reproducible tool to evaluate pain, several scoring systems have been introduced and utilized in critical care units. Validated scales include the CPOT (Critical Care Pain Observation Tool) and the BPS (Behavioral Pain Score). Both of these tools utilize objective and quantitative data. Although studies have shown that these tools are underutilized, when used appropriately, they have led to a decrease in the duration of mechanical ventilation as well as duration of ICU stay [7].

The CPOT assesses pain by evaluating patients on a scale of 0–2 on four different characteristics: intubation present (and if so, compliance with ventilator), facial expression, body movements and muscle tension. The highest score is an 8, and if the patient has a score ≤ 2 they are assumed to have minimal to no pain. However, if the score is >2 then they are assumed to have increased pain and should be treated accordingly. This scoring system is meant for reassessment at regular intervals, in order to monitor for trends and relative differences in the patient's scores over time. Patients excluded from using this scoring system include those who have undergone a heart transplant or thoracic aortic aneurysm repair, have an ejection fraction <25%, are receiving treatment for chronic pain or those who have dependence on alcohol or drugs [7].

The BPS evaluates pain by focusing on three behaviors and scoring them on a scale of 1–4. The characteristics evaluated include ventilator compliance, facial expressions and upper limb movements [7]. A score of <3 indicates no pain, 4–5 indicates mild pain, and 6–12 indicates inadequate pain control. This assessment should also be performed at regular intervals, ideally every 4–8 h.

20.5 Pain Assessment Tools (Tables 20.1 and 20.2)

Table 20.1 Description of critical care pain observation tool (CPOT) scoring

Indicator	Score	Description
Facial expression	0: Relaxed, neutral	No muscle tension observed
	1: Tense	Frowning, orbit tightening, tearful
	2: Grimacing	All movements above but also eyelids tightly closed, may be biting endotracheal tube
Body movements	0: Absence of movements or normal position	Does not move at all or appears to be in a normal position (no purposeful movement towards pain)
	1: Protection	Slow, cautious movement or rubbing the painful area
	2: Restlessness	Pulling on tubes, moving limbs or thrashing, not following commands
Compliance with the ventilator (if intubated) Or Vocalization (non-intubated patients)	0: Tolerating ventilator	Easy ventilation, no alarms
	1: Coughing but tolerating	Coughing, alarms may sound but stop spontaneously
	2: Fighting ventilator	Asynchrony, frequent alarms
	0: Talking in normal tone or no sound	No sounds at all or normal talking
	1: Sighing, moaning	Sighing, moaning
	2: Crying, sobbing	Crying out and/or sobbing
Muscle tension *Evaluation by passive flexion and extension of upper extremities when patient is at rest or while being turned*	0: Relaxed	No resistance to passive movement
	1: Tense, rigid	Resistance to passive movement
	2: Very tense or rigid	Strong resistance to passive movement or inability to complete testing

Adapted from Gélinas et al. [7]

Table 20.2 Description of behavioral pain score (BPS) scoring

Indicator	Score
Facial expression	1: Relaxed, neutral
	2: Partially tightened
	3: Fully tightened
	4: Grimacing
Upper extremities	1: No movement
	2: Partially bent
	3: Fully bent with finger flexion
	4: Permanently retracted
Compliance with the ventilator (if intubated)	1: Tolerating movement
	2: Coughing but tolerating ventilation most of the time
	3: Fighting ventilator
	4: Unable to control ventilation

Adapted from Gélinas et al. [7]

20.6 Treatment

Multimodal approaches continue to be the best option for pain management in critical care patients who are intubated. Given that patients who are in the ICU often have organ failure associated with their disease process, the clinician needs to be aware of the pharmacokinetic and pharmacodynamic characteristics of each drug. In addition, some patients may become hemodynamically unstable after adequate treatment of their pain due to blunting of sympathetic responses. Therefore, all medications should be administered and titrated slowly with careful attention to hemodynamics. Non-pharmacological methods should also be considered and implemented when possible, and interventional procedures can also be helpful in alleviating pain.

20.6.1 Non-pharmacological Management

Just as positioning while patients are under general anesthesia is paramount to avoiding injuries, appropriately positioning patients in the critical care setting is also important. This can be difficult, as patients are often unable to voice the pain they may be experiencing in a certain body part due to sedation, delirium, traumatic injuries or inability to communicate. When unable to effectively communicate, special care should be taken to follow the standard of care for body positioning in critical care patients [8, 9]. This guideline states that patients should be turned every 2 h and each position should be supported, especially at pressure points that are prone to skin breakdown. This becomes especially important when patients have a prior or current injury. However, if patients are positioned appropriately and comfortably, it

can decrease the likelihood of any new injury or painful area as well as prevent the formation of skin deterioration and ulcers.

Similarly to appropriate positioning, other straightforward non-pharmacological tactics can be utilized to aid in pain control. Heat or cold therapy has been recommended for use in the critical care setting. If able, patients should indicate which temperature is more helpful to them to help direct which modality should be used. These therapies should be implemented with caution in patients who are not able to communicate if an area being treated with cold or warm compresses is becoming too uncomfortable. Burns can occur in these situations, causing additional sequelae for patients.

In addition to adequate positioning, physical therapy also plays a pivotal role in assisting patient mobility while in the critical care setting. Immobility is the cause of multiple complications in hospitalized and non-hospitalized patients, so it is no surprise that movement through physical therapy has been shown to improve functional outcomes. There has even been evidence to support the use of physical therapy while patients are on the ventilator [10]. Often times, this treatment includes passive and/or active movements of extremities; however, ambulation has also been described in intubated patients. Physical therapists will frequently have a rubric to follow that is continuously adapted based upon each patient's performance. Providers need to be mindful that although physical therapy will almost certainly improve functional outcomes for patients, it will likely cause more pain in the short-term. Therefore, patients will often need to be pre-treated with pain medications in order to fully engage in their sessions.

Transcutaneous electrical nerve stimulator (TENS) units are available as another non-pharmacological method of pain management. These are small, battery-powered devices that deliver current through cutaneous electrodes that are attached to the skin and can relieve acute or chronic pain when placed near the painful area. They work to reduce pain by activating the large diameter, afferent nerves. The stimulation of these nerves then activate the descending inhibitory systems of the central nervous system, which in turn reduces hyperalgesia [11]. The literature includes variable results on outcomes of patients using TENS units in the critical care setting [11]. However, it is a therapy that is non-invasive, easy to use and inexpensive, so in many cases the possible benefit outweighs the risk and should be considered in cases of difficult pain control or somebody who has untoward side effects from their current pharmacological regimen [11]. Limitations of use include patients who are overly sedated or paralyzed, as this would not allow accurate programming of the TENS unit. The devices are normally programmed optimally when patients communicate that they are feeling non-painful stimulation in the affected area. Of note, patients who used a TENS unit prior to their hospitalization should continue if their cognitive status and other injuries allow.

Massage therapy is used in the outpatient setting for the treatment of chronic pain; however, it has not yet been universally adopted in the inpatient setting. However, recent studies have shown that massage therapy in ICU patients can lead to improved pain and anxiety levels [12]. In the studies observed, most patients had their upper and lower limbs massaged, as these were the most frequently accessible

parts of the body and patients did not require repositioning to undergo massage of their extremities. Other benefits noted included improved sleep quality, improved muscle tension and improved levels of consciousness. Limitations to the use of massage therapy in this setting include a lack of standardized practice with regards to the amount of pressure, the number of repetitions and the areas of the body massaged. Notably, therapists must pay careful attention to injuries the patient may have. In addition, as these patients are critically ill, it is not unexpected that multiple interruptions are likely to occur during a therapy session [12].

Acupuncture is a technique that is also used in the outpatient setting for the treatment of pain. Some studies have shown that it can be effective when used in the perioperative period as an adjunct for pain control and postoperative nausea [13]. Similar to the use of massage therapy, the evidence is lacking for its use in the critical care setting [14]. However, it is theoretically a cost-effective and safe option for patients.

An additional non-pharmacological method that has shown benefit is music therapy. This easy, low-cost and safe practice has been shown to decrease anxiety and pain levels in critical care patients [13]. Along with the decreased anxiety levels reported by patients, objective data such as respiratory rate, blood pressure and heart rate also improved after music sessions. There has even been evidence that a patient's respiratory rate may follow the tempo of the music and can be accordingly adjusted to a goal rate. Studies have also shown when patients are exposed to music therapy, their need for sedative medications decrease [15]. The optimal music choice for critical care and intubated patients has yet to be decided, but often if the patient is able to communicate, having them choose the music may be meaningful. However, the default is relaxation music with imagery (often played on the television) if the patient is unable to choose for themselves due to their medical condition.

Lastly, patients should be educated regarding the level of pain to expect for a certain injury or procedure. If a surgery is going to be offered to a patient, they should have an appropriate understanding of what the post-operative course should look like before the operation, including their levels of pain, physical therapy (if applicable), and what options there will be for treatment [16].

20.6.2 Pharmacological Management

Acetaminophen is often overlooked but can effectively contribute to pain control with lower side effects than opioids. Although not completely understood, acetaminophen's effects are thought to be due to interactions with serotonergic pathways in the central nervous system. Its reduction in temperature results from its effect on the hypothalamic heat-regulating system. There are several routes available for use, including oral, intravenous or rectal. When given orally, its onset of action is within 1 h, with a duration of 4–6 h. When given intravenously, the onset is within 5–10 min and has a similar duration to the oral formulation. The intravenous form is ideal for patients who have compromised colorectal function, as the

oral form is likely not to be well absorbed. However, recent studies have shown that in patients who have an intact gastrointestinal tract and are able to swallow, the oral form is just as efficacious [17]. The maximum daily doses for adults should be less than 4 g per day. For children, the total daily dose should be less than 75 mg/kg/day (not to exceed 4 g per day). Careful attention to maximum doses should be paid if a patient is receiving opioids that contain acetaminophen, as this can easily be overlooked, and a patient may unintentionally exceed their maximum dose. Hepatotoxicity is acetaminophen's major side effect and doses should be reduced in cases of hepatic failure or decreased liver function.

Non-steroidal anti-inflammatory medications (NSAIDs) such as ibuprofen and ketorolac should also be considered as an adjunct for pain control. Their primary mechanism of action is through inhibition of the cyclooxygenase enzyme, which results in decreased levels of prostaglandins. As prostaglandin is normally acts to mediate sensitization and facilitate hyperalgesia, these effects would be decreased when an NSAID is given. Ibuprofen and naproxen are administered orally but ketorolac is available in intravenous form. The major adverse effect this group of drugs has is its effect on the renal system. NSAIDs cause vasoconstriction of the afferent renal artery, which reduces renal blood flow and may lead to kidney injury. Therefore, dosages of these medications need to be adjusted in cases of renal impairment. Additionally, these medications lower thromboxane levels, which normally function to facilitate platelet activation; therefore, with the administration of NSAIDs there will be a decrease in these functions and a resulting increase in platelet dysfunction, leading to an increased risk of bleeding. Therefore, in patients that already have a bleeding disorder or at increased risk of bleeding because of procedures or recent surgery, the treatment team should use caution if choosing this class of medications. Usage of these medications should always be discussed with any surgical team involved. Topical NSAIDs such as diclofenac gel or a diclofenac patch can be a viable option, especially if pain is localized, as they have relatively little systemic uptake.

Anticonvulsants such as **gabapentin** or **pregabalin** are especially helpful in cases of neuropathic pain. Their use has been well validated in a variety of chronic pain disorders, such as trigeminal neuralgia and diabetic neuropathy. However, they have recently gained popularity in the acute pain setting with mixed results. Several studies have shown benefit, especially in cases where nerve injury may be a contributor to pain [18, 19]. If a patient was taking an anticonvulsant for pain prior to their hospitalization, it should be continued unless their current medical issues prohibit it. The exact mechanism is still not well understood but is thought to be through interaction at gamma-aminobutyric acid (GABA) or *N*-methyl-D-aspartate (NMDA) receptor sites. Side effects are mainly neurologic and frequently consist of sedation and/or dizziness, which can be heightened in the elderly population. Caution should be taken in the intubated population, who are often sedated to tolerate ventilation, but this side effect may be beneficial in decreasing doses of these other sedative medications. Additionally, as gabapentin and pregabalin are cleared renally, they should be dose adjusted in patients who have kidney disease or renal failure. Gabapentin and pregabalin are only available as oral medications; therefore, in an

intubated patient these medications either need to be crushed or the oral liquid formulation should be obtained and given via gastric or nasogastric tube.

Opioids are frequently used as first-line therapy for pain management. This is particularly true in the critical care setting. Opioids are often predictable, fast-acting and easily titrated. However, providers need to keep the Centers for Disease Control (CDC) guidelines in mind and use the lowest effective dose for the shortest period of time possible, even in the ICU setting. The most commonly used opiates in the critical care setting include fentanyl, hydromorphone and morphine, although there are many more available as intravenous formulations, such as methadone, meperidine, remifentanil, sufentanil and alfentanil. Oral options (which can also be administered via enteral feeding tubes) include oxycodone, hydromorphone, morphine, tramadol and methadone. Some of the oral options may also be combined with acetaminophen, therefore prescribers should be mindful if also ordering acetaminophen separately so as to not exceed the maximum dose of acetaminophen. Often doses are administered intravenously and on an as-needed basis; however, if pain is significant and unable to be controlled via this schedule one can switch to a continuous intravenous infusion or even a patient-controlled analgesic (PCA) option. If using a PCA, patients need to have appropriate mental status, which may not be the case for intubated patients, who are often sedated. Starting intervals for each option (fentanyl, hydromorphone and morphine) are often 8–15 min. Starting doses at our institution are 0.2 mg for hydromorphone, 25 mcg for fentanyl and 1 mg for morphine. These doses can be increased, or the interval shortened in a patient who has inadequate pain control with the current dose. Additionally, there are often boluses available to be given by the bedside nurses once or twice per hour at a dose that is up to double the patient-initiated dose, if needed.

Once patients are able to take meds orally (via nasogastric or orogastric tube), they should be started on an oral opioid for longer lasting coverage, while attempting to titrate off the intravenous formulation. Morphine and meperidine should ideally be avoided in critical care patients due to their active metabolites that can lead to untoward side effects such as neurotoxicity, especially in patients with renal dysfunction. Common side effects of opioids that should be expected are delirium, nausea and pruritis. However, more serious untoward effects may occur such as respiratory depression (less of an issue in intubated patients, but these adverse effects can counteract the goal of weaning off of the ventilator) or dependence. More rare but notable complications include serotonin syndrome, especially when given with other serotonergic medications, which are often ubiquitous in the critical care and perioperative setting. To minimize the risk of ileus and constipation, patients are often automatically started on a bowel regimen.

Topical **lidocaine** preparations are available, in a cream, ointment, or patch form. Topical lidocaine can be effective for localized pain, especially when applied around drain sites. If used, the prescriber needs to be mindful of other local anesthetics the patient may be receiving, especially through an epidural or regional catheter, so as to not exceed their maximum daily dose.

Lidocaine infusions are commonly used in the outpatient setting for patients who suffer from various chronic pain disorders. They are also sometimes used in the

intraoperative setting and are now being incorporated into several Enhanced Recovery after Surgery (ERAS) protocols, specifically for bariatric surgery, as an attempt to minimize opioid use. Studies looking at their use in the perioperative period have shown only mild to moderate improvement in pain scores with their use [20, 21]; however, if attempting to minimize the use of opioids this could remain an option to consider. When administered as a continuous infusion, patients need to be monitored closely for effects of toxicity, or LAST (local anesthetic systemic toxicity). Although the presentation of toxicity is widely variable, patients will often have progression from central nervous system effects, including altered mental status and seizures, to cardiovascular collapse. The treatment is to stop the offending agent and to administer intravenous intralipid solution, while following ACLS algorithms as necessary. To minimize the chance of this adverse complication, the prescriber should always calculate the patient's maximum dose using the patient's lean body weight. Additionally, patients who are pregnant or uremic should be administered a reduced dose. Caution should be used with patients who have hepatic failure and renal failure.

Ketamine, an antagonist at the NMDA receptor, is often considered in cases of refractory pain management and often in trauma patients where regional anesthesia may be contraindicated. When used in mechanically ventilated patients, its use has been shown to decrease the amount of opioids required to achieve pain relief [22]. It can be given as a continuous intravenous infusion or as intravenous boluses. It can also be compounded and administered topically or orally. Side effects are most frequently psychological in nature, with hallucinations being most common. If significant, dose adjustment or concurrent treatment with benzodiazepines may be required. Ketamine is preferred in patients who are hemodynamically unstable due to its minimal effects on hemodynamics and lack of respiratory depressive effects, though tachycardia and increased oral secretions are possible. There may be some concern regarding its use in patients with hepatic failure, but there is not enough strong evidence in this population to warrant absolute avoidance of this medication.

Dexmedetomidine has been used for intraoperative sedation, as an adjunct to general anesthesia, and for sedation in intubated patients. It is also helpful in preventing emergence delirium after general anesthesia in pediatric patients and is used for the treatment of acute alcohol withdrawal. It acts as an agonist at the alpha-2 receptor and has hypnotic and analgesic properties. Similar to ketamine, its use in intubated patients has been associated with a decreased need for opioids [23]. It is only available in the intravenous form, so it can be administered as a continuous infusion (as is common in the critical care unit) or as intermittent boluses. Its main side effects include bradycardia and occasionally alterations in blood pressure; both hypotension and hypertension have been recorded.

Another pharmacological method that has not yet been adopted in many settings is the use of **nitrous oxide**. Nitrous oxide can assist with analgesia in the intraoperative setting and has been used in a few obstetrical care units for pain in laboring patients. Ideally, it would be used for short procedures, such as bronchoscopy or chest tube placement [24]. Caution should be used in patients with pulmonary hypertension, altered mental status, known neurologic injury or in cases where

expansion of air-filled spaces can be detrimental. Again, as it has not been used ubiquitously the evidence is lacking, but this treatment modality may be increasingly available in the future.

20.6.3 Procedural Interventions

Regional anesthesia is preferred in patients who have an injury that is amenable to a regional technique without any contraindications. Options include neuraxial blockade or a peripheral nerve single-shot block or percutaneous catheter with ongoing infusion. Indications for regional anesthesia are often post-surgical and trauma patients. If the patient has undergone surgery, ideally the potential of such an intervention, either placed pre-operatively or post-operatively, should be discussed with the patient prior to surgery. This responsibility often lies with the team that will be placing the catheter, either the primary anesthesia team or an acute pain team. The decision of an epidural or nerve block should also be discussed with the primary surgical team. Other common indications for regional anesthesia include trauma patients. These patients often have rib fractures, which can be quite painful and compromise their respiratory mechanics, leading to complications such as atelectasis and infection.

Ideally, regional techniques decrease opioid consumption and the associated side effects of opioids, such as constipation/ileus, nausea/vomiting, and delirium or mental status changes. If the patient has a neuraxial or perineural catheter placed, they are often followed by an inpatient regional anesthesia team or the proceduralist who performed the intervention. One needs to be aware of the potential expected effects these procedures may entail. If the patient undergoes a neuraxial block, he or she may very well have some resultant hypotension afterwards due to the sympathetic blockade associated with these procedures. This hypotension can be even more exaggerated if the patient is hypovolemic. In addition, the block may make frequent motor or sensory examinations difficult or mask the development of undesirable complications from their trauma or surgery; these possibilities should be anticipated and discussed with the patient and the surgeon when considering a regional technique.

Regional anesthesia may be contraindicated in certain patients due to their anticoagulation status, coagulopathies, the presence of systemic or local infection, traumatic injuries and difficulties with positioning. There are some teams that will not perform neuraxial techniques if a patient is expected to remain intubated for a prolonged time in the post-operative period. A discussion should take place with the inpatient pain service or proceduralist regarding these expectations. Informed consent needs to be obtained from the patient or next of kin prior to proceeding with these procedures. Regarding anticoagulation and the appropriateness of performing neuraxial or peripheral procedures, one should refer to guidelines such as the American Society of Regional Anesthesia and Pain Medicine (ASRA) guidelines that were published in 2018 [25, 26].

20.7 Challenges in Management of Pain While in the Hospital

In general, critical care treatment teams aim to make patients as comfortable as possible while also trying to minimize sedation. As we have made this change in recent years, it is possible that we are undertreating pain in the ICU, which can lead to multiple complications such as chronic pain syndromes following discharge. Undertreatment of pain is multifactorial; however, the inability to accurately rate patients' pain while intubated likely plays a major role. Historically, this has been quite difficult, as communication remains a barrier to the proper evaluation of pain. It is the inaccurate belief that patients who are sedated are also obtaining pain relief and analgesia from that sedation that can contribute to the undertreatment of pain in intubated patients. With the validation of new scoring systems, it is hopeful that providers will be able to more accurately assess and therefore treat pain and the incidence of complications related to undertreatment or overtreatment will decrease.

Additional challenges to the treatment of pain are related to the limited number of pharmacological options available to patients, with critical care teams often relying solely on opioids. Although they are still the mainstay of treatment, we now have developed other pharmacological methods that target pain via various routes. Multimodal pain treatment can be effective while attempting to minimize adverse effects. These other treatment modalities also may have fewer side effects and minimize the risk of addiction. Furthermore, non-pharmacological methods are gaining popularity and recent studies have found them efficacious as well, especially when used in combination with medications. Finding the appropriate pain plan for a patient requires significant thought and individualized planning, as one treatment plan will not fit all patients. The care team needs to be aware of the multiple comorbidities patients may exhibit, especially in the intensive care setting, and the plan will likely need to be reassessed and adapted as comorbidities constantly evolve.

20.8 Management of Pain in the Inpatient Setting

A careful and thorough assessment of pain, ideally with input from the patient, is warranted. Even though patients who are intubated are likely to also be sedated, it is often possible to obtain some information regarding the patient's level of pain via validated assessments intended for use in the critical care setting, such as the Critical Care Pain Observation Tool (CPOT) or the Behavioral Pain Score (BPS). Treatment planning should also include consideration of pre-existing chronic pain, if applicable, the patient's comorbidities (which may be exacerbated, hence the need for intensive care level of treatment), and the patient's preferences.

Multimodal treatment should include both non-pharmacologic and pharmacologic modalities, when possible. Non-pharmacological techniques such as proper positioning, padding and turning, heat or cold therapy (being mindful that the patient may not be able to communicate if the compress is too hot or too cold),

physical therapy, TENS units, massage therapy, acupuncture, music therapy, and pre-surgical pain education and counseling are modalities that are typically low risk and may provide significant benefit to the patient. Pharmacological agents can also be utilized, though the patient's comorbidities and possible organ dysfunction should be taken into account. Mild to moderate pain should be treated with NSAIDs and acetaminophen, if not contraindicated. Topical medications such as lidocaine and diclofenac can also improve pain, especially if it is localized, such as a drain site or chest tube that causes pain. Adjunctive medications such as anticonvulsants (gabapentin, pregabalin) can also be considered; these medications are available in liquid form, and can be administered via enteral feeding tubes. Other infusions can sometimes be utilized, as well, such as lidocaine, dexmedetomidine, and/or ketamine. Nitrous oxide has even been occasionally used for short procedures in the intensive care setting. However, in the critical care setting, opioids are still considered the mainstay of pain treatment regimens, as they have reliable effects and intensive care teams are familiar with these medications. The selection of opiates should take into account the patient's organ dysfunction (particularly renal dysfunction), and the lowest effective dose should be used for the shortest amount of time.

If not contraindicated, interventional procedures such as neuraxial or peripheral nerve blocks or catheters can be considered, as these can decrease other medication side effects such as nausea/vomiting and ileus. However, hemodynamic stability, anticoagulation status/coagulopathies and concern for masking important symptoms or difficulty in obtaining an appropriate motor exam should be weighed when considering these options.

20.9 Discharge Plan for Pain Management

When patients are extubated and stepped down to a lower level of care, their pain management often changes due to several factors. The patient's treatment team will likely change, often causing a difference in opinion and options regarding pain management. Additionally, ideally their critical illness will have improved and pain as a result of their trauma, procedures while in the critical care unit or recovery from surgery will have diminished. A discussion should occur between treatment teams if a handoff is going to take place, especially if a patient's pain has been difficult to manage. Additionally, as pain improves, patients should be weaned from their medications, especially if they were started in the intensive care setting.

As opioids are often used as the standard of care for inpatient pain treatment, it is not surprising that many patients can develop tolerance to and dependence upon these medications. The DSM-IV definitions for opioid use disorders are discussed below. Tolerance is a pharmacological effect when the dose of a drug needs to be increased to accomplish similar effects. Dependence develops when abrupt withdrawal of the drug produces a constellation of symptoms referred to as abstinence syndrome. Addiction is a disorder that renders the patient without control of his or

her drug use and consists of preoccupation with the drug or other significant efforts to obtain the medication, despite personal harm or ill effects. Given that some patients are on continuous infusions or repeated doses of opioids for several days and even weeks, this increases the risk of development of these disorders and the weaning process may become even more difficult. Withdrawal is an obvious concern and should be monitored for and treated appropriately. When patients transfer to the general care floor, the team assuming care should also understand these risks.

As patients recover from their critical illness, their pain should improve and the amount of outpatient medications being prescribed should be low. If patients are sent home with an opioid prescription, it should be the lowest amount possible (within reason) with the goal of tapering off in a limited amount of time. An outpatient provider who is experienced in tapering of opioids should follow them closely.

Occasionally, patients may see a chronic pain physician as an outpatient. If this is the case, a chronic pain inpatient team may be consulted to make recommendations based on their outpatient regimen. This team does not exist in every inpatient setting but can be utilized if it does. They may also be in contact with the patient's outpatient provider or primary care physician and facilitate setting up appointments with a pain specialist following discharge if necessary.

20.10 Summary

- Pain management in critical care patients who are intubated is fraught with difficulty, ranging from difficulties when adequately attempting to quantify their pain to choosing the appropriate pain management plan while keeping in mind their hemodynamic status and comorbidities.
- Patient co-morbid medical conditions, such as kidney and liver dysfunction, should be followed closely in the critical care setting; treatment planning should take these potentially dynamic changes into account.
- Risk factors for development of chronic pain disorders after untreated acute pain include previous pain disorder, prior opioid use, and significant untreated pain for long periods of time.
- There are several scoring systems used to assess pain and guide treatment. The most validated systems include the CPOT and BPS systems.
- Non-pharmacological treatment options exist and should be attempted when applicable. These include physical therapy, massage therapy, TENS units, acupuncture and music therapy.
- Multimodal approaches to pain management are always preferred and include pharmacological treatment with opioids, NMDA antagonists, alpha-2 agonists, NSAIDs and anticonvulsants.
- Interventional procedures such as regional anesthetic blocks and catheter placement can also provide significant relief while minimizing opiate and other medication use, thereby minimizing side effects.

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Chapter 21
Navigating Familial Opioid Use Addictions and Socially Complex Situations in the Treatment of Acute and Chronic Inpatient Pain

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21.1 Introduction

When evaluating an inpatient who has required opioids and may be discharged with a prescription for them, asking about a patient's family members may seem beyond the scope of work as a consultant. While the national opioid crisis has been extensively discussed in the media and the academic literature, it can feel challenging to know how to reconcile this broad social trend with the specific individual and family. However, from both the perspective of the individual patient and family, and through a public health lens, safe opioid prescribing and careful assessment of family-related risk factors is essential to prevent the risk of a patient's legitimate pain medication prescription becoming a medication source for a family member with a substance abuse problem. This chapter will focus on navigating a consult for safe prescribing of opioids to prevent opioid misuse by individuals other than the patient to whom the medication is prescribed.

When evaluating any patient on opioids, the potential for opioid misuse by other individuals, also known as diversion, should be considered [1]. This diversion can occur as a result of a patient sharing medication with family members willingly or as a result of theft. Note that in this chapter we will use the term "family member" as shorthand for a variety of individuals with the potential to be affected by or involved in diversion, including family members, friends, significant others, and roommates. Among individuals misusing opioids, over 50% report having obtained their last pills from a friend or relative—the most common single source. Individuals whose family members have been prescribed opioids have nearly three times the risk of an opioid overdose requiring medical attention, with increasing doses of opioids correlating with further risk of overdose in family members who were not recipients of the opioid prescription [2]. Although large-scale genetic research into OUD is in its early stages, there are a number of genes related to dopamine and opioid receptors and brain-derived neurotrophic factor that have been implicated in a genetic role for transmission

of opioid use disorder (OUD), suggesting both a biological and environmental basis for the disorder [3, 4].

This chapter is particularly relevant to clinical scenarios in which the risk for diversion may be of greater than average concern, including:

- Known OUD in a patient's family member
- Situations where a patient's family member has a known history of opioid use disorder can be particularly challenging in terms of balancing the patient's need for analgesia with concern about the risk of misuse in a family member. A family member's history of OUD may only be obtained through careful questioning by the practitioner, highlighting the importance of taking a family history that includes questions about substance abuse.
- Family members without known OUD but with other risk factors for developing one, including other substance use disorders and untreated psychiatric disorders [5]
- Comorbid illnesses in family members raise the risk for those individuals going on to develop a new OUD. It can be difficult here to find the right balance between acknowledging the epidemiological risk without further stigmatizing this already vulnerable population.
- Patients with a history of misuse or diversion themselves
- A previous history of medication diversion elevates the risk for diversion again in the future and raises similar concerns about balancing legitimate pain needs with the risk that this behavior could pose to the patient, family members, and the broader community.
- Cancer pain and hospice care. In this scenario, both the large quantity of medication provided and family administration of opioids to the patient are potential risk factors. This is known to be a high-risk situation for diversion regardless of what is able to be determined about the patient and family history.

Even in these socially complex situations, where the risk for diversion is higher than average epidemiologically, there can still be uncertainty about how to proceed with care and pain management. Given the stigma around substance abuse and mental illness, patients may be unaware of their family members' difficulties, including psychiatric history and this is required by most states in the practice of pain medicine. Preparing and educating providers to understand the need to assess the risk for diversion and family-related complications from opioid prescriptions is an essential first step from the standpoint of both patient safety and patient education.

21.2 Ethical Considerations

The treatment of acute and chronic pain in socially complex situations involving a high risk of diversion of controlled substances or risk of potential harm to individuals and their families creates a number of ethical considerations. The

questions raised revolve around how a clinician should balance treating their patient, while also considering the risks of others around that patient, specifically:

- To what extent can a physician or provider consider familial and societal harm in the assessment of a patient?
- Is there a violation of the doctor-patient relationship if a physician or provider's treatment plan is influenced by external factors beyond the patient's needs?
- To what extent can and should a physician or provider assess familial risk factors in the treatment of a patient's pain?
- To what extent can and should a physician or provider involve family members in these discussions while a patient is hospitalized?
- Is it ethical to investigate risk factors associated to a patient's family by engaging with family members' medical providers, institutions or registries?

Similar questions have been raised in the setting of other complex social issues affecting familial units such as alcohol use disorder, firearms in the home, smoking, and sexually transmitted diseases. As the study and evidence in harm reduction has progressed over the past decades, so has our understanding of the role played by physicians and providers. While there are strong considerations in maintaining the privacy of a patient's family members or partners, medical, social and legal institutions now all recognize the necessity to consider and assess these complex situations as a way to prevent harm to society. Given the significant public health burden created by opioid use disorder in the status quo, to not consider elements of familial and social context like the risk of diversion would be akin to not considering a patient's partner's HIV status prior to discussing birth control options. Opioids provide an additional nuance to other substance abuse situations as simple avoidance of the drug in an inpatient or outpatient setting as a means of harm reduction may not be possible in the treatment of acute or chronic pain.

One of the most widely utilized frameworks for ethical modeling in medicine is the four principles construct by Beauchamp and Childress. Table 21.1 summarizes each principle as it applies to the assessment and treatment of pain in the setting of complex social and familial situations.

The framework highlights conflicts between the four ethical principles, namely the balance between autonomy and justice to do what's best for both the patient and the people/society surrounding that patient. Each physician will have to weigh these various principles to see what she or he is comfortable enacting, bearing in mind that these complex ethical scenarios rarely ever have a "right" answer. Nevertheless, our overall recommendation is it is within the ethical scope of practice for a physician to assess a familial history of OUD to develop a more patient-centered pain regimen that also prioritizes the safety of other family members, if the information is gathered in an ethically defensible manner.

Table 21.1 Summary of principles related to the treatment of pain, family, and complex social issues

Principle	Principle defined	Principle applied
Autonomy	A respect for the freedom and the privacy of a patient as it concerns their ability to determine their medical care	– Patients may not be willing to discuss opioid use disorders within their social contexts – Family members may not want their drug use history to be assessed – Retrieving information from other providers, registries, or institutions may violate HIPAA as providers are not explicitly tasked with caring for family members – Private information about family members may be recorded or leaked during assessment – Treatment decisions made with concern for a larger social context may conflict with the patient's desired treatment plan
Beneficence	A consideration to perform acts in the best interest of the patient	– Treatment that aims to reduce harm in a larger social context may or may not be in the direct best interest of the patient or their pain
Non-maleficence	A consideration to do no harm	– Treatment that aims to reduce harm in a larger social context strongly conforms to the principle of "do no harm" as the provider is consciously avoiding action that may harm the patient or others
Justice	To balance care provided for a patient within the larger context of societal needs	– Given the clear public health risks associated diversion or misuse of opioids in familial units and the moral imperative of physicians and providers to reduce these risks, the assessment and treatment of pain necessitates inclusion of risk reduction methodology – Engaging with patients and their families prior to the initiation of treatment plans may lead to a deeper understanding of a patient's social context – Utilizing strategies to decrease the possibility of diversion may decrease rates of addiction, relapse and overdose in familial and social units close the patient

21.3 Risk Stratification

In addition to clarifying the patient's individual medical, social, and psychiatric histories, asking questions to understand the circumstances and histories of a patient's main family members can be important in determining which situations may pose a greater than average risk for diversion. This process of risk stratification includes questions that assess the risk level more directly and those that offer a broader context for prescribing.

The process of risk stratification can start with open-ending questions that are initially broad but progressively more specific, with the aim of gathering informa-

tion about what the patient understands about the addictive potential of opioids and whether the patient has any concerns about specific family members. These open-ended questions may lead to more specific interest on the clinician's part in any one of these more specific areas:

21.3.1 History of OUD in Family Members

Some patients may identify that particular family members are known to have misused opioids. In these cases, the clinician should identify which specific family members have been affected, whether the opioid misuse is current or past (and if past, how long ago the use stopped), whether that family member's illness included prescription diversion including diversion from the patient's home, whether that family member has had an overdose, any treatment history for the family member, and how close the affected family member is in terms of relationship and geography.

21.3.2 Other Comorbid Disorders in Family Members

Some patients may deny a history of OUD in family members, while also reporting a history of other mental illnesses and a history of psychiatric disorders. It is important to expand your understanding of this to the extent possible given the high co-occurrence of OUD and other psychiatric disorders. It is helpful to ask specifically about alcohol or other substance use disorders, untreated psychiatric disorders (with bipolar disorder and schizophrenia in particular associated with elevated risk of developing opioid use disorder), history of suicide attempts and completed suicides in the patient's family, and untreated chronic pain. Assessing the patient's knowledge of family member's OUD and other co-occurring disorders is helpful in determining to what extent the patient might directly or inadvertently contribute to diversion. Explicit education around the risks for family members may be necessary in patients who acknowledge a relevant family history but with limited insight. In addition to helping understand the potential for difficulties in the patient's family members, this will also expand your understanding of the patient's own environmental and genetic risk factors for developing OUD.

21.3.3 Living Situation

When beginning discharge planning early in the inpatient admission, the patient's living situation should be clarified as soon as possible as part of the risk stratification process. Stressful living environments for patients and families, in particular financial and housing instability but also a wide range of psychosocial stressors, have been shown to contribute to the incidence of OUD [5]. Specifically, this

includes knowing what kind of housing the person lives in and how secure it is, the exact people the patient lives with and individuals who spend a significant amount of time in the home, and to what extent family members with OUD are in the home and potentially have access to the patient's opioid medications.

21.4 Inpatient Stay as a High-Risk Period

The inpatient setting can present particular challenges in terms of incidence of OUD in patients and their family members, or relapse in individuals with a history of this. Opioid doses are often increased during hospitalizations, leading to risk of dependence in the individual receiving them and increasing the likelihood of higher amounts of medication being prescribed at discharge. The process of opioid switching to balance analgesic and adverse effects as doses are increased, may lead to inpatients being started on medications that have a higher potential for abuse in the outpatient setting [6]. Additionally, family members of patients have the opportunity to observe the effects of these medications, which can prompt their curiosity about the medications in terms of the family members' own untreated or undertreated chronic pain, and the non-analgesic pleasing effects of opioids. This one-sided positive experience of opioids obscures the risk of dependence and abuse.

Stress has been shown to increase the risk for OUD, and for most individuals the inpatient setting is a uniquely stressful environment. Patients experience stress related to the condition that brought them to the hospital and any ongoing undertreated pain, and family members experience physical dislocation, employment-related difficulties, and seeing their loved one in pain and often in a medically precarious state. Observing the level of individual and family stress and discussing any emerging concern as a treatment team is essential.

The logistics of the hospital can also create particular risk. Despite significant advances in controlling the administration of opioids, medications are at times improperly administered or discarded, creating opportunities for access outside the prescribed times and amounts. Family members who are considering diversion may abuse Patient Controlled Analgesia (PCA) pumps to create an artificial impression of high opioid demand, leading to more prescribed medication at discharge; these pumps must be monitored as carefully as possible to prevent misuse. Frequent discussion of opioid dosing and administrations may trigger cravings in family members with current OUD or a history of it.

21.5 Psychosocial Interventions

Involving family members in discussions about opioids specifically and outpatient management of chronic pain more generally can be critical in reducing the incidence of OUD. Higher levels of familial cohesion have been associated with reductions in the onset of other substance use disorders [7]. At the most basic level, this

starts with education for the patient and family members about the safe management of opioids, the warning signs of an emerging use disorder, and resources for seeking professional help in the event of a complication related to opioid prescribing.

21.5.1 Family-Based Interventions

As a provider, it is helpful to know about the resources that are available to families in which at least one individual is contending with a substance use disorder. These resources are particularly useful in cases where a patient has told a provider about a family member's substance use disorder, but the provider is not directly treating that person. Al-Anon and Nar-Anon are two organizations with thousands of individual groups in the United States and around the world which apply the 12-step model to create a sense of community and provide support for individuals whose family members have substance use disorders [8]. The Johnson intervention (which has inspired the idea of having an "intervention" for a troubled family member in the common imagination) is a clinician-supported method in which families are coached on how to directly confront their loved one with a substance use disorder, an approach which has some success in engaging those individuals in treatment [9]. More recently, the Community Reinforcement and Family Training (CRAFT) model has emerged as an alternative to 12-step groups. CRAFT is a form of family therapy that offers participants behavioral techniques (such as positive reinforcement and a specific communication model) to use with the individual who is abusing substances, with the goal to convince that person to enter treatment—a goal not shared by other models. CRAFT is effective in increasing engagement in substance-related treatment by the individual who is using substances [10].

21.5.2 Individual Interventions

Individual interventions at the level of the patient or a family member at risk of OUD can take many forms. Standard substance-specific psychotherapies, often cognitive-behavioral therapy (CBT) or motivational interviewing (MI) are widely available, offered at a variety of levels of intensity (from weekly visits to day treatment models with several hours of group and individual treatment daily), and generally covered by insurance. Providing resources for individuals with comorbid substance use disorders and other psychiatric disorders can be challenging, since many treatment centers focus only on one or the other and may exclude individuals with a comorbid condition. One simple provider intervention is to offer all patients and families contact information for the Substance Abuse and Mental Health Services Administration Helpline (1-800-662-4357), which can be called 24 h a day and offers free, confidential referrals to substance abuse and mental health treatment providers in the caller's area (SAMHSA). Involving the hospital's psychiatric

consultation-liaison service to discuss local treatment options that team is familiar with may be helpful in more challenging cases.

21.6 Safe Prescribing Guidelines

There are a number of strategies that can be utilized both in the inpatient setting and in discharge planning to minimize of diversion or to families when dealing with complex social situations involving opioid use disorders.

21.6.1 Inpatient

21.6.1.1 Abuse-Controlled Environments

When the risk of diversion from a patient to a family member is relatively high in an inpatient setting, the first recommendation is to ensure the safety of all by having the patient in a monitored setting. Staff should be trained to monitor for signs of overdose, including respiratory insufficiency, excess sedation, an unprotected airway and other adverse reactions to opioids for both the patient and associated family members. Nursing to patient ratios may be adjusted depending on the level of risk involved or appropriate alternative staff may need to serve as one-to-ones. Appropriate staff members may also be trained to provide emergency reversal treatment, such as intravenous or intranasal naloxone. Special care should be given in the delivery and the discarding of leftover medications, specifically that controlled substances should never be left unattended in the room and excess intravenous medication should be emptied as free liquid into the appropriate medication waste receptacles, not thrown in bags and syringes that can be retrieved.

21.6.1.2 Safe Initiation of Opioid Treatment

In 2016, the Center for Disease Control (CDC) released a guideline for prescribing opioids that emphasized that opioids are not a first-line therapy for individuals who suffer from chronic pain [11]. Prior to initiating opioid therapy, both nonpharmacologic therapy and nonopioid pharmacologic therapy should first be used and proven ineffective at relieving pain (see section below). Furthermore, clinicians should establish realistic treatment goals for patients and emphasize the potential risks associated with opioid use and misuse. Patients should fully understand the risks associated with opioid therapy and the responsibilities that the patient has in managing their therapy to mitigate these risks [12]. Many medical licensing boards and other regulatory bodies have encouraged and, in some cases, even mandated written pain treatment agreements that acquire informed consent from the patient, increase

patience compliance, and reduce the potential for misuse [13]. These pain treatment agreements not only emphasize the responsibilities of both the health care provider and patient, but they also include the conditions under which the patient's opioid treatment will be terminated. The National Institute on Drug Abuse (NIDA) provides multiple sample patient agreement forms that clinicians can use prior to initiating long-term opioid therapy [14].

In addition to having these patients sign a paint treatment agreement, it is essential for clinicians to establish clear patient-provider communication and provide considerable resources that educate the patient and their family on opioid use and misuse [15]. The CDC provides an opioid factsheet that it recommends distributing to patients who are prescribed opioids for both acute and chronic pain [16]. Providing resources such as this to patients and their family members is important to emphasize the importance of the not sharing the medication with others and properly disposing of any unused pills [17]. When appropriate, providers should initially prescribe immediate-release opioids, which are less likely to lead to dependence when compared to long-acting opioids [18, 19]. It is equally important that clinicians prescribe patients the lowest effective dosage to minimize side effects, including the risk for misuse.

When prescribing opioids for acute pain, providers should prescribe the quantity required to relieve the expected duration of pain and not longer. In a retrospective database study of more than one million opioid naïve patients undergoing surgery, the strongest predictor of opioid misuse was the total prescription duration [20]. Therefore, clinicians should prescribe opioids for the shortest duration necessary and restrict the prescription refills that patients can receive [21]. Research has demonstrated that a 3-day course is the most effective timeframe to administer these medications, since most instances of acute pain are relieved within this time. Additionally, after only 5 days of prescription opioid use, a patient's risk of developing a long-term opioid dependence drastically increases [22].

While short-term use of opioids does not typically require the assistance and monitoring of clinicians, the termination of opioids after long-term use is more complicated. Upon the cessation of long-term opioid use, many patients experience symptoms of withdrawal that can be debilitating and dangerous. One way to mitigate these unwanted withdrawal symptoms is to slowly taper the opioid dose. There is no single protocol used for how a clinician should taper the dose, although most outpatient detoxications utilize a slower tapering protocol to minimize side effects and increase patient compliance. With these protocols, it is common to swap from a short-acting opioid to an extended release opioid and slowly taper the dose over several weeks [23].

21.6.1.3 Abuse-Controlled Delivery Mechanisms

Patient Controlled Analgesia (PCA) pumps have become widely available for the administration of controlled substances in inpatient settings for intravenous, epi-

dural, intrathecal and peripheral nerve catheters. PCA pumps for controlled substances should have a locking feature so that medication reservoir is not open to the patient. Additionally, many may have alarms for tampering such that the system may stop if the external tubing is manipulated with excess medication being drawn off the line. However, there may still be gaps in these alarms; one example is if the medication tubing is disconnected from the patient, allowing the medication to be diverted directly from the line. Thus, a care provider should be regularly available to assess and document the device for both the integrity of the line and the information displayed by the device. Other examples that should raise concern for device tampering include:

- When the reservoir or "Volume to Be Infused" (VTBI) is depleted faster than expected from what is displayed on the pump, despite accounting for intermittent bolus administration
- When multiple alarms go consistently go off when members of the care team are not present
- When patient's receives bolus dosages as early as available consistently throughout the hospital stay, despite endorsing and displaying clinical findings of adequate pain control

Use of epidural, intrathecal or targeted peripheral nerve catheters when clinically indicated for post-operative pain may allow teams to decrease the concentration of opioid medication utilized in the medication regimen, while also taking advantage of the synergistic effects of local anesthetics in pain management. In situations where there are attempts made at tampering with the PCA device and it is no longer advisable to keep the device present in the room or if a PCA is not available, the care team may need to proceed with an alternative delivery mechanism. Here we recommend utilization of alternative opioid administration that is less prone to diversion and misuse, including the use of abuse-deterrent opioid formulations, opioid patches and/or intermittent IV boluses by nursing staff that can ensure appropriate delivery.

21.6.1.4 Abuse-Deterrent Opioid Formulation

Recently, the development and promotion of abuse-deterrent opioid formulations presents a novel strategy to decrease the misuse of prescribed oral opioids. As of July 2019, the FDA has approved seven non-generic opioid medications as containing abuse-deterrent properties:

- OxyContin (oxycodone ER)
- Embeda (morphine + naltrexone ER)
- Hysingla ER (hydrocodone ER)
- MorphaBond (morphine ER)
- Xtampza ER (oxycodone ER)
- Arymo (morphine ER)
- RoxyBond (oxycodone IR)

These abuse deterrent formulations (ADFs) contain physical and/or chemical properties to prevent against administration through unintended means (e.g., chewing, nasal snorting, smoking, and intravenous injection). ADFs primarily prevent abuse through three mechanisms: A. physical or chemical barriers (typically polyethylene oxide) that resist either mechanical damage or chemical dissolution of the pill B. an agonist-antagonist combination where the antagonist is typically not absorbed into the bloodstream when ingested, but will be released systemically when snorted or injected and/or C. an additive compound described as an aversive agent, that makes unintended usage of the medication less desirable through side effects like nausea or burning of the nasal mucosal membranes. These changes are mainly designed to prevent abuse in individuals who are tempted to transition from oral to more intense use (nasally or IV).

All the aforementioned medications present various nuances in understanding their ADF properties. For example, abuse of OxyContin in its original ER formulation was rampant, prompting its manufacturer to reformulate the drug in 2010 with a polyethylene oxide (PEO) coating that prevents mechanical crushing and turns the pill into a viscous gel when interacting with liquid solvent to prevent snorting or IV injection. In 2013, the FDA issued new policy stating that all generic OxyContin competitors would need similar ADF properties to receive FDA clearance. Embeda, on the other hand, is a combined morphine and naltrexone formulation, where the naltrexone is activated only if the pill is taken in unintended ways. Naltrexone is placed in the core of the pill and coated with an impermeable membrane that sequesters the drug from absorption if taken orally; only when this membrane is broken via tampering does the naltrexone mix with the morphine counteracting the agonist mechanism of action.

Given that ADF technology is still relatively new to the market, it is unclear whether it will achieve its ultimate goal of deterring unintended use of opioid medications; however, RADARS (The Researched Abuse, Diversion and Addiction-Related Surveillance system) data has indicated that as these ADF technologies have come to market there has been immediate and significant reductions in overdosage rates. In this regard, these technologies help in deterring unintended routes of administration; family members with OUD can still have negative consequences from oral use of these medications. Additionally, the evidence to suggest that ADFs reduce unintended routes of administration is conflicting. Studies comparing unintended use of original versus reformulated OxyContin showed that ADFs do reduce, but do not eliminate abuse of the drug. Further, despite ADFs being available since 2010, a study in 2015 showed 96% of all opioid medications prescribed lacked ADF properties, highlighting gaps in practice and health policy. Finally, ADFs may themselves present negative externalities to patients. In 2017, the FDA issued a statement that an approved medication at that time, Opana ER (oxymorphone ER), had been associated with the development of thrombotic thrombocytopenic purpura in individuals who had abused that medication, amongst other side effects, leading to the medication ultimately being taken out of the market.

Overall, ADFs may represent a new strategy to aid clinicians in decreasing certain kinds of abuse with opioids and warrant further study to understand how they may be utilized to better manage acute and chronic pain.

21.6.1.5 Multimodal Analgesia

In socially complex situations where diversion or family OUD may be prominent, the use of multimodal analgesia to decrease the usage of opioid medications may greatly prevent harm, while adequately treating the patient's pain. Prior to initiating opioid therapy, both nonpharmacologic therapy and nonopioid pharmacologic therapy should first be used and proven ineffective at relieving pain. Furthermore, clinicians should establish realistic treatment goals for patients and emphasize the potential risks associated with opioid use and misuse. Patients should fully understand the risks associated with opioid therapy and the responsibilities that the patient has in managing their therapy to mitigate these risks. Many medical licensing boards and other regulatory bodies have encouraged and, in some cases, even mandated written pain treatment agreements that acquire informed consent from the patient, increase patience compliance, and reduce the potential for misuse. These pain treatment agreements not only emphasize the responsibilities of both the health care provider and patient, but they also include the conditions under which the patient's opioid treatment will be terminated. The National Institute on Drug Abuse (NIDA) provides multiple sample patient agreement forms that clinicians can use prior to initiating long-term opioid therapy.

21.7 Here We Briefly Highlight Multimodal Options to Guide Care Teams

- Ketamine—Also a controlled substance with abuse potential that may carry its own risk of diversion.
- Local anesthetic/Regional anesthesia when applicable for acute surgical pain
- Acetaminophen
- NSAIDs
- Precedex
- Neuropathic adjuncts (Gabapentin, TCAs and SSRIs)
- Transcutaneous Electrical Nerve Stimulation (TENS)
- Peripheral Nerve Stimulation (PNS)
- Outpatient/Discharge Planning

21.7.1 Opioid Discharge Planning

In the context of high-risk family OUD or diversion, outpatient opioid prescribing represents an area where the care team plays a critical role in harm reduction. Common strategies to reduce harm include prescribing shorter courses of opioids, ensuring that the patient has to contact the care team for repeat prescriptions and

allowing providers to reassess the patient's pain. Further, the patient should also be provided with a multimodal regimen to limit opioid needs, if possible. Another strategy is to limit prescribing breakthrough opioids with a high potential for diversion and abuse by reviewing hospital opioid utilization to better assess for outpatient needs and convert the patient to opioids with ADFs or opioid patches. Physicians and providers must take care, however, in prescribing long acting opioids for the treatment of acute pain as this may result in increased opioid dependency and induced hyperalgesia over time as the patient's acute pain needs diminish. Finally, teams must balance the benefits of lengthier inpatient stays where the patient's acute opioid regimen can be tapered off and a number of interventions can be enacted to prevent diversion with the risks of longer hospitalizations that include an increased risk for infections and resource utilization.

21.7.2 Outpatient Referrals and Testing

Involving consultants that may provide benefit to patients in complex social situations during their inpatient stay may allow for earlier planning and a higher rate of compliance with the outpatient regimen. For patients being sent home with multimodal regimens, longer acting narcotic medications with ADFs, or patches, an inpatient referral to pain management may help smooth the transition from inpatient to outpatient settings. Further, if a physician or providers discussion with the patient or the family results in concern for outpatient diversion or harm, a referral to outpatient addiction specialist or social/behavioral services for the family member may reduce the risk of harm. For patients or families that have already been affected by opioid overdoses with residual trauma or supportive needs, teams can facilitate recovery by referring to groups that provide counsel and resources. Finally, the patient should be briefed that if diversion is a concern, outpatient urine toxicology may be warranted, especially with the provider who will be continuing to manage the opioid usage.

21.7.3 Safety at Home

To ensure that any opioids being prescribed to the patient will be utilized correctly and safely, patient education and planning are of the utmost importance prior to discharge. Recent studies suggest a significant rise in the inappropriate use of opioids including death from accidental overdose and diversion in the US over the last decade [24]. The care team should ensure the patient and the family fully comprehend the medication regimen at the time of discharge and how it may have been altered from pre-hospitalization. Patients should be advised to keep controlled substances away from medication closets where multiple family members may have access. Depending on the familial situation, patients may benefit from storing medications in a lock box or safe where only the patient or a highly trusted care

provider like a visiting nurse or home health aide, who is solely aware of the combination or password [25]. Patients should also be given specific directions on how to dispose of opioid medications when they no longer require them as long-term storage of leftover pain medication has been associated with diversion, the development of OUD, and even death in family members. Options to discarding opioid medications include take-back/mail-back options at certain pharmacies or flushing unused pills down a toilet or sink. Finally, if a clinical suspicion of harm is high enough in complex familial OUD situations, physicians or providers should consider training patients and their families on the use of emergency narcosis reversal with intranasal naloxone kits. It may be prudent habit for care teams to prescribe naloxone concurrently with a patient's discharge opioid regiment.

21.8 Summary

- Familial opioid disorders and other socially complex situations can present great challenges to patients, their families and to care teams during and after hospitalizations.
- If concerns are brought up about family members with OUD, resources should be made available to help that family member deal with substance use disorders.
- Addiction disorders affect people across all socioeconomic backgrounds, race, age and gender.
- Families of all types can also be affected and no assumptions should be made about the type of families that are affected by addiction and substance abuse disorders [26]. Addictions and substance abuse disorders can be severely stressful, disruptive and even traumatic for all the members involved.
- For care teams looking to guide patients and their families who have already lost someone to substance abuse or addiction, the GRASP (Grief Recovery after a Substance Passing; grasphelp.org) is one network that provides counseling and community-facing services.
- It is imperative that care teams orient themselves to the correct resources and strategies to reduce the societal harm that results from opioid misuse and diversion.

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Chapter 22
Patient with Sickle Cell Disease

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22.1 Introduction

Sickle cell disease (SCD) is the most common inheritable hematologic disorder globally with the highest prevalence occurring in sub-Saharan Africa, Spanish-speaking regions in the Western Hemisphere, Saudi Arabia, India, and the Mediterranean [1]. In the United States there are an estimated 100,000 patients living with SCD. African-Americans see the highest rates with an estimated one case of SCD per 365 births [1]. The physician's role in the care of the patient with sickle cell disease is of particular importance as there are few diseases in which morbidity and mortality can be as profoundly impacted with proper treatment. An intricate understanding of the disease is essential for the treating physician to properly care for these patients, as the most minute mistake may quickly prompt massive medical emergencies or even prove fatal. This chapter will provide a contemporary understanding of the pathophysiology, genetics, complications, and varying treatment approaches involved in providing optimal care for patients with sickle cell disease.

Prior to modern advances in medicine, those with SCD rarely made it out of childhood—with improvements in direct treatment as well as diagnostic and

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preventative measures, major strides have been made in this area. The largest studies conducted on SCD patients have shown an average lifespan approximating four decades of life with women living an average of 6 years longer in one study, and 4 years longer in the other [2, 3]. Though these are the largest studies to date, they are certainly becoming outdated with end-dates of 1988 and 2005. More recently, in 2016 a series of case studies were published documenting SCD patients living well into their eighties [4]. Quality of life in these patients has also seen immense improvements with current medications able to substantially reduce the incidence of some of the most debilitating complications of SCD, namely acute chest syndrome, pain crises, and the need for blood transfusions [5]. These advances are staggering and show the vast potential treating physicians have in extending and improving patient's lives given a proper understanding of the intricacies of the disease and optimization of care.

22.2 Pathophysiology and Diagnosis

In order to understand the pathophysiology of SCD, it is first important to review the structure of hemoglobin. Hemoglobin, the oxygen carrying unit of red blood cells, is a tetramer consisting of two alpha subunits with the remaining two subunits varying with the specific type of hemoglobin. Though there are various types of hemoglobin, there are two that play the largest role in sickle cell anemia, the predominant fetal form (HbF) as well as the predominant adult form (HbA_1). HbA_1 consists of two alpha subunits and two beta subunits. Sickle cell anemia arises when either both copies of the gene that encodes for the beta subunits carry a point mutation resulting in a substitution of glutamate for a valine residue in the final beta-globin product or one copy carries this mutation and the other copy carries a separate mutation. This leads to high levels of a form of hemoglobin, denoted HbS, with poor solubility when deoxygenated, thus rapid polymerization occurs in conditions of low oxygen tension It is important to note that other circumstances mimic low oxygen tension by promoting deoxygenation of HbS, namely states of dehydration, acidosis, as well as infection. The end result is a deformation in structure of red blood cells from their usual biconcave disk shape to a crescent-like, or "sickle", shape (Fig. 22.1). On the other hand, fetal hemoglobin lacks these defective beta subunits and instead utilizes two gamma subunits. This explains why those with sickle cell anemia do not typically experience symptoms in-utero or within the first 5–6 months of life when high amounts of fetal hemoglobin continue to persist [6]. It is also an important concept in the treatment of SCD as the primary medication used, hydroxyurea, aims to increase levels of fetal hemoglobin in circulation.

In its simplest terms, the pathophysiology and inherent complications faced by SCD patients can be traced back to four phenomena exhibited by sickled red blood cells: morphological limitations in their ability to flow through microvasculature, increased rigidity, increased presence of surface adhesion molecule, and increased fragility [7]. While normal red blood cells traverse the microvasculature in an

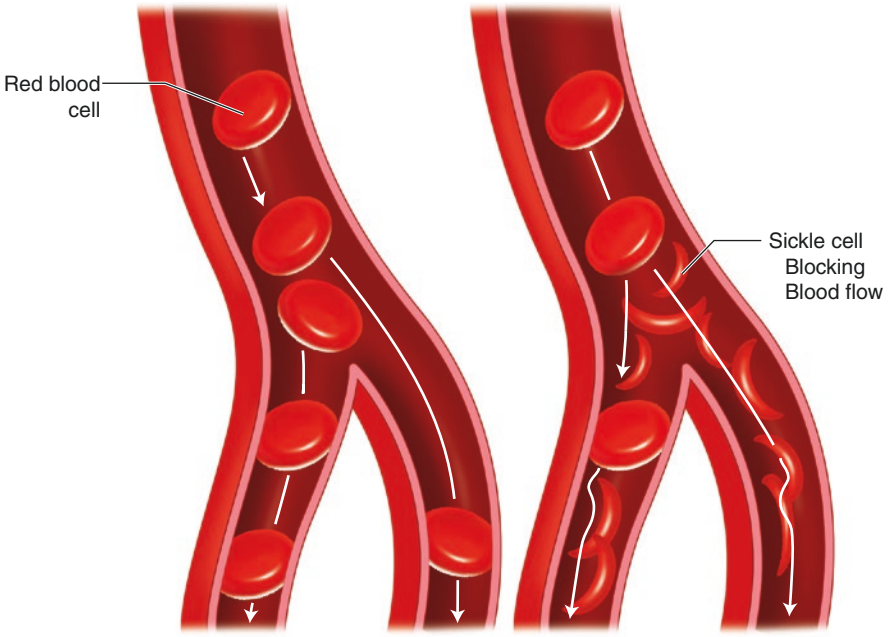

Fig. 22.1 Sickle cell anemia

orderly and uninterrupted fashion, sickled red blood cells display a shape and increased rigidity which is far less conducive to orderly flow which results in the occlusion of vasculature. Red blood cells in patients with sickle cell anemia have also been observed to express more surface adhesion molecules promoting increased adhesion to surface endothelium and furthering their vaso-occluding tendencies [7]. Vaso-occlusion manifests as bouts of pain that may occur anywhere in the body persisting for hours to weeks, these events are termed *vaso-occlusive crises*. End-organ damage including cerebrovascular events, ischemic strokes, intracerebral hemorrhages, acute chest syndrome (ACS), pulmonary hypertension, retinal infarcts, splenic infarcts, and progressive multiorgan dysfunction syndrome may also present as a result of vaso-occlusion [8].

While many of the acute manifestations of SCD can be attributed to vaso-occluding events, the increased fragility of red blood cells also presents a major challenge to affected patients. As previously discussed in this section, red blood cells in SCD patients shift from their regular biconcave disk shape to their sickle form in conditions that promote deoxygenation of HbS. These red blood cells revert back and forth between these two forms depending on the local environment. This chronic shifting of formation leads to increased red blood cell fragility eventually leading to hemolysis. Hemolysis of red blood cells in SCD not only significantly decreases their half-life, leading to anemia, but the resultant release of free hemoglobin also impairs proper endothelial function by depleting nitric oxide stores [9]. Increased fragility is not the only factor that plays a role in the decreased lifespan of red blood cells as splenic sequestration is also involved. The end result is

substantial as demonstrated by the fact that normal red blood cells have an average lifespan of 90–120 days whereas the red blood cells of sickle-cell anemia patients have an average lifespan of 10–20 days [9]. The resultant anemia can be profound, leading to a litany of symptoms including fatigue and impaired growth. In an attempt to compensate, the bone-marrow becomes hyperactive producing increasing numbers of red blood cells and reticulocytes to provide adequate tissue oxygenation. This is of particular importance as this compensatory measure may be compromised in scenarios of bone-marrow suppression. An example is parvovirus B19 infection which can quickly become life-threatening as may lead to *aplastic crisis*.

Another major concern when managing patients with sickle-cell anemia is the susceptibility to infection. The spleen is vital in clearing bacteria, particularly encapsulated bacteria such as *streptococcus pneumoniae* and *haemophilus influenzae*. In SCD, repeated episodes of vaso-occlusion and microinfarcts lead to progressive fibrosis and atrophy of the spleen, rendering it non-functional. Typically, this process of autosplenectomy, is complete by age 5 in most patients [10]. Accordingly, SCD patients require careful attention in regards to vaccination schedules as well as perioperative care, further details of which will be provided later in this chapter.

22.3 Variants of Sickle Cell Syndromes and Genetics

Sickle cell disease is the most common hemoglobinopathy in humans as well as the most commonly heritable hematologic disease [11]. A sickle cell disease is an autosomal recessive condition that results when the sickle mutation (HbS) is inherited alongside an additional mutation in a globin gene. Rather than having HbA_1, a point mutation in the beta-globin subunit of hemoglobin, leads to a dysfunctional beta-globin that results in the sickle cell shape. The major variants in the other hemoglobin allele have different clinical manifestations and will be discussed below. Less common variants such as Sickle-Alpha-Thalassemia, Sickle-Hereditary Persistence of Fetal Hemoglobin, Sickle-Delta Beta (0) Thalassemia, Sickle-Hb Lepore Disease, Sickle Hb-D Disease, and Sickle Hb-E Disease will not be discussed.

22.3.1 Homozygous Sickle Mutation (HbSS)

In HbSS, an individual inherits two abnormal sickle cell genes (HbS), one from each parent. This mutation generally has the most severe manifestations because both hemoglobin genes are irregular, leading to chronic hemolytic anemia and subsequent effects. There are both acute and chronic manifestations of sickle cell disease. Acutely, clinical manifestations are the result of infection, anemia, and vaso-occlusion, while chronic manifestations are the result of chronic organ ischemia and infarction [12]. Signs of disease occur early in life around 5 months of age

once fetal hemoglobin becomes depleted and is replaced by sickle hemoglobin [13]. HbSS is often referred to as sickle cell anemia.

22.3.2 Sickle Cell Trait (HbAS)

Sickle cell trait (SCT) results from inheriting a single sickle cell allele along with a normal HbA_1 allele. In this state, individuals are considered benign carriers and usually do not present with any symptoms. Rarely, SCT patients may experience symptoms with certain environmental changes such as increased atmospheric pressure, low oxygen levels in the air, dehydration, and at high altitudes [14]. Because of the presence of one normal allele of the beta-globin gene, individuals with sickle cell trait have normal complete blood cell counts and peripheral blood smears. It is more common in areas such as sub-Saharan Africa, parts of India, the Middle East, and Mediterranean countries because SCT appears to have a protective effect against malaria caused by plasmodium falciparum [15]. However, individuals with sickle cell trait are able to pass the gene to offspring and should be counseled accordingly.

22.3.3 HbSC Disease (HbSC)

This form of sickle cell syndrome results from the inheritance of one sickle cell allele and one abnormal hemoglobin C allele (HbC). With HbC in the cell, there is enhanced and prolonged potassium and chloride cotransport with subsequent loss of potassium from the red blood cell, termed "red cell dehydration." Combined with increased intracellular concentrations of HbS, this promotes the polymerization, sickling, and symptoms seen in HbSC Disease [16, 17]. This usually results in a disease that is more severe than sickle cell trait, but milder than sickle cell anemia [18, 19]. Common findings include mild hemolytic anemia (hematocrit >28%), elevated reticulocyte counts, slowly progressive splenomegaly, and target cells on peripheral blood smear [20]. Functional asplenia can also occur in many individuals with HbSC disease, increasing susceptibility for infection with encapsulated organisms [21].

22.3.4 Sickle-Beta-Thalassemia (HbS B-Thalassemia)

In beta thalassemia, mutations in the beta globin gene can result in impaired production of beta globin chains in the hemoglobin tetramer. This leads to an imbalanced ratio of alpha to beta globin, which can impair maturation of red blood cells and lead to ineffective hematopoiesis [22, 23]. Unpaired alpha globin chains are unstable and can precipitate within the cell, leading to various clinical manifestations [24]. Sickle-Beta-Thalassemia results from the inheritance of a sickle cell allele and a beta-

thalassemia allele. The severity of the disease depends on the nature of the beta-thalassemia mutation, defined as either sickle cell-beta^0 thalassemia or sickle cell-beta$^+$ thalassemia. In sickle cell-beta^0 thalassemia, there is the complete absence of HbA_1 production which results in a more severe course than in sickle cell-beta$^+$ thalassemia [25].

22.4 Acute Crises

While there have been significant strides in the management and treatment of sickle cell disease, SCD patients can suffer from chronic inflammatory vasculopathy and acute crises which can result in organ dysfunction [26]. One of the hallmarks of SCD is acute episodes of pain from vaso-occlusion of blood vessels that often requires hospitalization [27]. These painful episodes of "sickle cell crisis" can be seen in infants starting from 6 months of age and may follow SCD patients throughout their lifetimes [27, 28]. Several types of crises fall under the umbrella of sickle cell crisis and will be discussed below.

22.4.1 Vaso-Occlusive Crisis

Vaso-occlusive crises make up a large portion of patient encounters due to SCD, with over 90% of children diagnosed with SCD at birth experiencing an episode of pain by the age of six [28, 29]. These episodes occur due to properties of the sickled red blood cells leading to inflammation, increased rigidity of RBCs, and vascular endothelial cell adhesion. The cycle of vaso-occlusion results in local hypoxia and release of inflammatory mediators [30]. Patients often present in moderate to intense pain that may be accompanied by fever, although the frequency and intensity of pain episodes may be variable [30, 31]. The most common sites of pain from a vaso-occlusive episode include the chest, back, abdomen, and extremities, although pain can also manifest from other parts of the body [30]. There may be specific triggers for some patients, such as wind, low humidity, poor air quality, stress, low nocturnal oxygen saturation in children, dehydration, alcohol, and menses [32–37]. Many patients manage their pain at home, but it is imperative to conduct a thorough evaluation to rule out potentially life-threatening complications of SCD that may be masked by sickle cell pain [28, 38, 39].

22.4.2 Splenic Sequestration Crisis

The spleen is a commonly affected site of vaso-occlusion because of its narrow vessels and the subsequent intrasplenic trapping of red blood cells. Patients with SCD present with acute, painful, and rapid enlargement of the spleen

accompanied by an acute drop in hemoglobin level despite elevated reticulocyte counts [28, 40–42]. It is possible for the spleen to sequester a large portion of the total blood volume and therefore increasing the risk of hypovolemic shock and death [30]. Mortality rates are up to 10–15% and up to half of those who survive a splenic sequestration crisis experience a recurrent sequestration [40, 41].

22.4.3 Aplastic Crisis

During aplastic crisis, the bone marrow temporarily fails to produce red blood cells. Because patients with SCD have a shortened red cell lifespan and a lower baseline hemoglobin, this can result in a rapid drop in hemoglobin levels associated with reticulocytopenia [30]. It is most commonly triggered by parvovirus B19, which invades proliferating erythroid progenitors in the bone marrow and suppresses RBC production. Patients can present with sudden pallor and weakness from chronic hemolysis [30].

22.4.4 Acute Chest Syndrome

Acute chest syndrome (ACS) presents as a syndrome of fever, chest pain, cough, wheezing, hypoxemia, or respiratory distress in the setting of new radiodensity findings on chest radiography [30, 43]. It occurs in up to 50% of patients and is the leading cause of death in SCD [2]. ACS episodes can be commonly triggered by bone marrow or fat emboli in adults leading to hypoxia, adhesion of sickled red blood cells to the pulmonary vasculature, as well as further cycling of hypoxia and sickling [30, 44]. The causes of ACS can be multifactorial, but the etiology either triggers a vaso-occlusive event (ie, asthma, hypoventilation, infection) or results from vaso-occlusion itself, such as in the case of bone marrow and fat emboli [45, 46]. Patients can progress to respiratory failure and death if not treated appropriately and aggressively [44].

22.4.5 Hyperhemolytic Crisis

Hyperhemolytic crisis is characterized by an acute drop in hemoglobin levels despite increased reticulocyte production. Patients will present with acute anemia with evidence of accelerated hemolysis [43]. The etiology and pathophysiology behind hyperhemolytic crisis is not well understood, but can be potentially fatal if not addressed rapidly [47, 48].

22.5 Treatment

The management of sickle cell disease is centered around preventing complications, rapidly treating complications that arise, and the potential role for curative treatment with hematopoietic stem cell transplantation. Due to the unique considerations of patients with SCD, the management of patients presenting with sickle cell crisis, post-surgically, and in the emergency department will also be discussed.

22.5.1 Preventing Complications

Establishing care with a clinician and treatment team is an important part of routine health maintenance of SCD for prophylactic measures, education of patients and their families, and individualized treatment. Patient and family education allows for more autonomy in managing the disease and recognizing symptoms that need early attention and intervention. Patients with SCD under the age of 5 are treated with penicillin prophylaxis and appropriate immunizations to prevent infections [49]. Furthermore, the Advisory Committee on Immunization Practices (ACIP) provides up-to-date vaccination schedules with specific instructions for patients with SCD. Notably, there are special vaccination schedules for encapsulated bacteria such as *Haemophilus influenza type b*, *streptococcus pneumoniae*, and *Neisseia meningitidis*.

Hydroxyurea and L-Glutamine are the only Food and Drug Administration (FDA) approved treatments for the prevention of vaso-occlusive events in sickle cell disease. Hydroxyurea works by increasing levels of fetal hemoglobin (HbF), which inhibits the polymerization of the sickled hemoglobin [50]. It has also been shown to improve survival and reduce complications of SCD [51–53]. Hydroxyurea is recommended in symptomatic infants <9 months, clinically severe SCD in children and adolescents, and adults with more than three painful episodes in the last year or more than three episodes of ACS in the last 2 years [54]. However, the recommendation for hydroxyurea should be balanced with the US boxed warning about side effects of bone marrow suppression and secondary malignancy, along with the time needed to see benefit with treatment (3 months). There is also evidence for the use of hydroxyurea in combination with L-glutamine, a conditionally essential amino acid, which becomes deficient in the body under stress [55]. In a 2018 randomized trial, L-glutamine was shown to be associated with fewer acute pain events, fewer hospitalizations, fewer days in the hospital, and fewer patients with acute chest syndrome, independent of concomitant hydroxyurea use [56].

22.5.2 Treatment of Complications and Pain Management

Treatment of SCD complications relies upon recognition of the underlying process causing severity. Complications of SCD should be treated accordingly, such as treating vaso-occlusive events with pain medications, treating infections with

antibiotics, and providing transfusion therapy for chronic anemia. The treatments of the various sickle cell crises will be discussed below.

Patients with SCD should be educated on preventative steps to reduce the frequency of pain crises. These include behavioral and environmental alterations such as staying hydrated, maintaining thermoregulation, avoiding high altitudes or low oxygen levels, as well as pharmacotherapy with hydroxyurea [13]. However, pain is not completely avoidable and remains a challenge for patients. The level and frequency of pain varies between patients and can be acute or at times lead to chronic pain. It is recommended that patients should be reassessed frequently regarding their pain, and that patient's self-reported pain should be the primary source of pain assessment [57].

The American Pain Society (APS) and the American Academy of Family Physicians recommends the following regarding pain management [57]:

- Aggressive pain management to reduce pain and support patients in attaining maximal functional ability
- Use of analgesics for pain, tailored for each patient
- Nonsteroidal anti-inflammatory drugs or acetaminophen in the management of mild to moderate pain, unless contraindicated
  - The addition of an appropriate opioid if pain persists
  - Appropriate tapering of opioid therapy is recommended to reduce withdrawal syndromes
- Severe pain in a patient with SCD should be considered a medical emergency and managed as such.

22.5.3 Curative Treatment

The only curative treatment for SCD is allogeneic hematopoietic cell transplantation (HCT). Indications for HCT include symptomatic vaso-occlusive events that are not well controlled with medication and progressive organ dysfunction. However, this is generally limited to adolescents with a matched related (often sibling) donor and there are significant risks associated with this procedure. The decision is highly individualized and risks and benefits should be discussed among the patient, family, and care team [58].

22.5.4 Treatment of Sickle Cell Crisis

While there have been marked improvements in the treatment of sickle cell disease, patients with SCD still suffer from acute crises in addition to chronic inflammatory vasculopathy. SCD crises are associated with high morbidity and mortality; therefore, it is essential to promptly recognize the risk factors and presentation to manage patients appropriately [26]. Recommendations for

interventions from the National Heart, Lung, and Blood Institute Expert Panel Report (2014) have been summarized in the Table 22.1 below. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to determine the strength of recommendations and grade the quality of evidence [49].

Table 22.1 Interventions for the management of acute crises in sickle cell disease

Acute crisis	Intervention[a]	Strength of recommendation	Quality of evidence
Vaso-occlusive crisis	Analgesic treatment within 30 min of triage or 60 min of registration, typically with opioids	Consensus	Panel expertise
	Rapid treatment with parenteral opioids for severe pain	Strong	High
Splenic sequestration crisis	Immediate IV fluid resuscitation if patient is hypovolemic	Strong	Low
	Transfusion to raise hemoglobin to stable level if patient has severe anemia	Strong	Low
	Splenectomy if recurrent episodes or symptomatic hypersplenism	Moderate	Low
Aplastic crisis	Immediate red blood cell transfusion to restore hemoglobin to safe value	Consensus	Panel expertise
	Required isolation of hospitalized patients to prevent spread of parvovirus B19	Consensus	Panel expertise
Acute chest syndrome	Hospitalization	Consensus	Panel expertise
	IV cephalosporin, oral macrolide antibiotic, and supplemental oxygen	Strong	Low
	Simple blood transfusion if hemoglobin concentration is >1.0 g/dL below baseline	Weak	Low
	Exchange transfusion with rapid progression defined by: O_2 saturation <90% on supplemental oxygen ↑ respiratory distress ↑ pulmonary infiltrates ↓ hemoglobin concentration despite simple transfusion	Strong	Low
Hyperhemolytic crisis[b]	Transfusion with compatible blood [12, 48]		

[a]Packed RBC units utilized for transfusion should be HbS negative, leukoreduced, and fully matched for C, E, and K antigens [26, 49]

[b]Hyperhemolytic Crisis was not discussed in the 2014 report and recommendations have been summarized from other sources

22.6 Management of Pain in the Inpatient Setting

22.6.1 Perioperative Management of Sickle Cell Patients

Perioperative care in SCD patients is centered around the prevention of vaso-occlusive events and their downstream manifestations (VOCs, stroke, ACS). Surgery requiring general anesthesia presents a challenge in these patients as adverse events are common if proper preoperative measures are not taken. Previous studies have shown adverse sickle-related events occurring in up to 18.6% of surgical cases when preoperative care was not carried out [59]. Increasing oxygenation in SCD patients has proven to be effective in preventing adverse postoperative sickle-related complications. Current guidelines indicate that all patients with HbSS and HbS-β^0 thal should undergo simple transfusion in order to bring Hgb levels up to 10 g/dL for low and medium risk procedures. High-risk surgeries such as neurosurgery are less clear and sickle-cell expert should be consulted to determine the proper transfusion therapy on a case by case basis [54]. HbSC patients have lower rates of sickle-related complications during surgery and thus may not always require preoperative transfusions. It is recommended that HbSC patients should only undergo preoperative transfusion if they have asthma or have had previous serious acute sickle-related complications such as strokes or acute chest syndrome [60]. Partial exchange transfusion therapy may be preferable in HbSC as some of these patients may present with Hgb levels >10 g/dL, in these cases it is recommended that HbA levels be brought to >50% or HbS <30% prior to surgery [60]. Proper preoperative hydration should also be emphasized in SCD patients.

Postoperatively, it is vital to maintain proper oxygenation during sedation and upon waking incentive spirometry should be utilized throughout the recovery period [61]. Pain in the postoperative setting should be properly evaluated to distinguish acute postoperative pain from sickle-related sources of pain such as VOCs or previously existing chronic pain attributable to the disease as this can help in determining pain management course [62]. Sickle-related pain will likely be apparent as it is typically more intense than acute postoperative pain. The first line treatment for this pain is opioid therapy with dosing based on previous episodes. Ketorolac should be avoided in these patients as to prevent renal injury and no form of cold compress should be utilized as it may precipitate sickling. For pain refractory to opioid therapy, ketamine has proven to provide relief. Acetaminophen is a more conservative approach that may also be helpful in some cases though there is less evidence supporting this [62].

22.6.2 Management of Sickle Cell Patients in the Emergency Department

Emergency department physicians must be well equipped to deal with SCD patients as this is the setting in which they are most likely to present. The Sickle Cell Data Collection (SCCD) collected data on California residents and found late teen to

middle-aged SCD patients present on average 3 times a year for sickle-related complications [63]. The most common cause for presentation is severe pain crises refractory to treatment administered at home. As previously discussed, an individualized treatment plan dependent on the patient's particular constellation of symptoms as well as current analgesic usage should be deployed. The components of these plans are included earlier in this chapter (see Table 22.1). While the use of IV fluids may seem logical in these patients, it should be noted that fluids should not be administered if hydration status is appropriate as there is evidence that this may lead to atelectasis and increase the risk of developing acute chest syndrome [64].

Just as with the general population, SCD patients are susceptible to acute pain conditions, such as those that follow polytraumatic injuries in motor vehicle accidents [65, 66]. While the acute pain management of such scenarios should be similar to that employed for non-SCD patients, some notable considerations should be made to optimize outcomes for SCD patients.

Firstly, it is imperative to ensure that the acute presentation is appropriately diagnosed [65, 66]. The incorrect diagnosis of an acute pain condition as being an acute crisis may serve detrimental by delaying care of the true underlying etiology. Such misdiagnoses are possible given the risk of recall bias in SCD patients with frequent acute pain crises and hospitalizations. Additionally, if a true acute pain condition not related to an acute crisis is diagnosed, practitioners must still maintain a low threshold of suspicion for the subsequent development of an acute crisis. Given that acute crises can sometimes develop in response to traumatic injuries, early and appropriate diagnosis of secondary acute crises can serve to optimize pain management and outcomes. Standard and conventional management strategies including judicious use of IV fluids can serve to mitigate risk of secondary acute crises.

Treating acute pain conditions in SCD patients should be in accordance to the injuries sustained [65–67]. In those SCD patients suspected to have opiate use disorders, opiate medications should be utilized with caution but not withdrawn in settings of severe trauma. There is no contraindication to the use of intravenous or oral opiates in the appropriate clinical contexts. Additionally, there have been no associations made between opiate or non-opiate analgesic medications to risk of sickling. In persons with high opiate use for chronic SCD pain or current respiratory compromise, judicious use of opiates and careful monitoring is warranted to prevent risk of toxicity [67]. Nonetheless, optimizing the use of non-opiate medications, such as acetaminophen and NSAIDs, as well as non-pharmacologic modalities is prudent. Note that use of cold temperature modalities, including cold packs, may precipiate vaso-occlusive crises and patients with such treatments warrant careful monitoring.

The use of regional anesthesia in SCD patients has limited evidence [61, 68]. Given theoretical risks of regional hypoperfusion to the targeted area, regional anesthesia interventions have been thought to be associated with SCD specific adverse effects. However, the current data exploring this phenomenon appears to be unclear. In a small cohort of SCD patients undergoing cesarean sections, spinal anesthesia was found to be non-inferior to general anesthesia in producing vaso-occlusive cri-

ses [69]. It was also found that those who received spinal anesthesia had fewer opiate requirements post-operatives, lesser blood loss, and better neonate outcomes. Vuong et al. reported successful use of a femoral nerve block to provide meaningful pain relief in an adolescent SCD patient undergoing proximal femoral necrosis [70]. High level and high-quality evidence supportive of regional anesthesia in treating acute pain conditions in SCD patients are lacking.

Ocular trauma should be evaluated rapidly to determine if hyphema is present. Hyphema is particularly dangerous in SCD patients as they are unable to tolerate the resultant moderate rises in intraocular pressure and optic atrophy may result [71]. If even trace amounts of blood are seen in the anterior chamber this should be considered an ophthalmologic emergency and specialty care should be consulted [72].

22.7 Discharge Plan for Pain Management

1. Family and social support
2. Access to psychological support
3. Follow up care—with hematology and, as appropriate, chronic pain management
4. Prescriptions and counseling for chronic pain management
5. Compliance with SCD pain crisis prophylaxis medications, as dictated by hematologist
6. Non-pharmacological modalities for pain management i.e. heating packs and massage therapy
7. Counselling regarding chronic pain in SCD and appropriate management of acute crises

22.8 Summary

- Physicians play a critical role in supporting and educating patients throughout the steps of the SCD process.
- Unique precautions for managing SCD patients in acute pain crises, perioperative setting, and emergency room care are needed.
- Having an understanding of the disease processes and associated complications is critical in recognizing symptoms, administering appropriate management, and optimizing patient care.
- Opiates are often appropriate in treating vasoocclusive pain crises and acute pain conditions. However, non-opiate medications and non-pharmacological options should be optimized as conjunctive therapy.
- There is no clear evidence for using regional anesthesia to treat acute pain in SCD patients. There is some thought that regional anesthesia produces local hypoxia and can precipitate sickling.

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Chapter 23
Patient with Multiple Sclerosis (MS)

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23.1 Introduction

Multiple sclerosis (MS), an immune-mediated demyelinating disease of the central nervous system (CNS), is one of the leading causes of debility in adults. The prevalence of MS varies from 100 per 100,000 in North America and Europe to 2 per 100,000 in Eastern Asia and sub-Saharan Africa populations [1] primarily affecting middle aged (20–50 years old) women at a 3:1 female to male ratio [2]. A range of neurological and musculoskeletal symptoms may occur in patients with MS including cognitive dysfunction, gait impairments, depression, spasticity, fatigue, pain, and visual disturbances.

Pain has been shown to have variable rates of prevalence in patients with MS. A systematic literature review by Foley et al. and O'Conner et al., found up to 63% and 50% of patients with MS experienced a form of pain, respectively [3, 4]. The most common acute manifestations of pain in this population include headaches, back pain, and arthralgias [5]. Foley et al. studied the prevalence of symptoms in MS patients. Forty-three percent of patients experienced headaches, 26%

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encountered neuropathic extremity pain, 20% suffered from back pain, 16% experienced Lhermitte's phenomenon, 15% complained of muscle spasms, and 4% experienced trigeminal neuralgia [3]. Causing adverse effects on quality of life and functionality, management of pain in MS patients is critical. The varied presentations of pain symptoms often require multimodal pharmacological and interventional therapies.

23.2 Pathophysiology

To better understand and manage pain in MS patients, we must first understand the disease itself. The etiology of MS is largely unknown; however, the most widely accepted theory is that autoreactive lymphocytes initiate inflammation and neurodegeneration leading to demyelination of the CNS [6]. Destruction of the myelin sheath causes delayed conduction velocities and results in impaired communication within the CNS, leading to the debilitating symptoms of paresthesias, weakness, spasticity, and pain.

Pain in multiple sclerosis patients can be classified into four categories based on their pathophysiology: *neuropathic pain or pain directly related to MS, nociceptive pain or pain indirectly related to MS, mixed neuropathic and nociceptive pain, and MS treatment-related pain* [5].

Neuropathic pain occurs as a result of direct damage or inflammation of the axons after demyelination of the central nervous system has occurred [7]. This type of pain can be characterized as intermittent, constant, spontaneous, or triggered. The most common type of pain is dysesthesias, which are burning or aching sensations. Dysesthesias are best managed with anti-seizure agents, anti-anxiety agents, and tricyclic antidepressants. Other neuropathic pain syndromes in MS patients include trigeminal neuralgia and Lhermitte's phenomenon.

Trigeminal neuralgia (TN) presents as unilateral, intermittent, sharp, electric-like pain in the distribution of one or more branches of the trigeminal nerve, with the maxillary branch being the most commonly affected. Episodes are typically triggered by non-painful stimuli including light touch, brushing, chewing, talking, and smiling. It is managed with anti-epileptic, anti-spastic, and anti-anxiety medications. First line management is carbamazepine, an anti-epileptic agent inhibiting sodium channels preventing repetitive and sustained action potential firing [8]. Second line treatment option includes lamotrigine, an anti-epileptic agent inhibiting sodium channels stabilizing neuronal membranes and modulating neurotransmitter release [9]. In severe cases, in which the patient has minimal relief with pharmacological agents, surgical procedures including microvascular decompression to relieve local pressure on the trigeminal nerve may be considered.

Lhermitte's phenomenon is classified by episodes of stabbing neck pain that travels from the head down to the spine which occurs with cervical spine flexion.

The main pathophysiological reasons for this phenomenon are demyelination and hyperexcitability present at the level of the neuron [10]. Often, Lhermitte's sign may be an indication of an MS exacerbation or relapse. It is typically managed non-pharmacologically with a soft neck collar preventing forward flexion of the neck [7]. Pharmacologically, physicians may prescribe steroids to manage MS flairs, subsequently resolving Lhermitte's symptoms [6].

Nociceptive pain occurs indirectly due to the disability from MS. This includes optic neuritis, headaches, and musculoskeletal pain. Optic neuritis occurs when there is inflammation of the optic nerve. This can lead to symptoms including painful eye movements and vision changes. Treatment of optic neuritis involves anti-inflammatory agents, classically corticosteroids. Headaches, specifically migraines and tension-type headaches, are very common in multiple sclerosis patients. Migraines are suspected to result from disturbances in sensory processing [11]. Primarily, migraines are managed with non-steroidal anti-inflammatory drugs (NSAIDs) and triptan class agents. For refractory or complex migraines, local botulinum toxin injections may be considered.

Musculoskeletal pain often occurs in MS patients due to deconditioning, immobility, and weakness [7]. There may also be a component of osteoporosis which may be precipitated or worsened with the use of steroids to manage the course of the disease. Prevention is critical in managing musculoskeletal pain with exercise and calcium and vitamin D supplementation [7]. In an inpatient setting, this includes initiating physical therapy early on to help with ambulation, stretching, and strengthening [7]. Pharmacological agents used include NSAIDs and muscle relaxants.

Mixed neuropathic and nociceptive pain present as spasticity. Affecting up to 90% of patients with MS, spasticity is a clinical manifestation of an upper motor neuron lesion [12]. It is physiologically defined as velocity-dependent increase in muscle tone caused by the increased excitability of the muscle stretch reflex [12]. Clinically, spasticity manifests as increased muscle resistance to passive stretching [12]. Increased excitability at the muscle stretch reflex is due to abnormal activity at the level of the muscle spindles and extrafusal muscle fibers which occurs due to primary lesions in the CNS leading to subsequent reduction in spinal inhibitory pathways [12].

Spasticity is a major source of pain and impairs activities of daily living. Without adequate management, the progression of spastic tone can contribute to the formation of debilitating contractures, joint dislocations, and pressure ulcers [13]. Spasticity is managed with multimodal therapies including physiotherapy and medical management including baclofen. In severe cases, intrathecal baclofen or botulinum toxin injections can be considered.

Treatment related pains can occur including injection-site reactions, steroid-induced osteoporosis, and degenerative joint disease. Injection-site reactions can be managed with proper injection techniques and local cooling at injection site. Systemic adverse effects of drugs including interferon beta causing myalgias can be managed with ibuprofen or naproxen [7].

23.3 Diagnosis

Diagnosis of multiple sclerosis is on the basis of dissemination of CNS lesions in space and time and to rule out other diseases which present similarly to MS [14] (Fig. 23.1). There are no diagnostic laboratory markers for MS. However, clinical history, neurological examination, imaging, and cerebrospinal fluid (CSF) analysis aid in confirmation of the disease [14]. A new attack can be identified by new onset of neurological deficits lasting greater than 24 h with an identifiable lesion on magnetic resonance imaging (MRI) in the absence of other infectious etiology. One of the most important diagnostic tools used in the confirmation of MS is CSF testing. This test helps differentiate infectious causes from non-infectious, inflammatory disorders. In MS, CSF protein levels are normal or slightly elevated, normal pressures, and normal glucose levels. Additionally, the CSF/serum albumin concentration gradient (Qalb) is normal or slightly elevated, reflecting permeability at the blood brain barrier (BBB) [14]. Qualitatively, the presence of oligoclonal IgG on

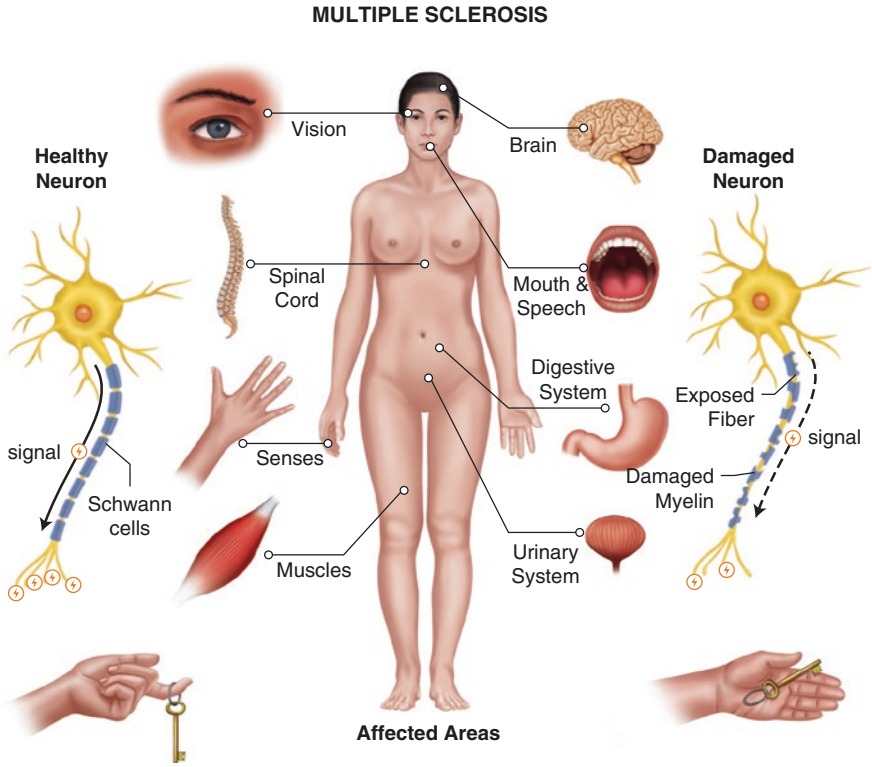

Fig. 23.1 Affected areas in patients with multiple sclerosis

serum and CSF electrophoresis is seen in 80–90% of MS patients. However, the presence of oligoclonal IgG is not pathognomonic for MS.

Now, to adequately manage pain in MS patients, the correct syndrome must be diagnosed. The diagnosis of pain syndromes is clinically diagnosed based on the signs and symptoms stemming from the various pathophysiologic pathways discussed above. Often, laboratory testing and imaging are not useful in making diagnoses. Practitioners should rely on obtaining a comprehensive history to identify the pain syndrome present.

Dysesthesias are a manifestation of neuropathic pain resulting from direct presence of plaques in the central nervous system [8]. This interferes with transmission of signals to and from the brain resulting in abnormal sensations. Dysesthesias are clinically diagnosed as sensations can be characterized by patients as mild tingling, sharp, stabbing, or burning pain [8]. Different types of dysesthesias exist depending on site involved: scalp, cutaneous, and oral dysesthesias. No laboratory testing or imaging has been shown to aid in the diagnosis of dysesthesias.

The diagnosis of TN is primarily clinical with episodes of pain within the distribution of the trigeminal nerve. Based on the clinical history, if TN is suspected, it is important to search for secondary causes. Common secondary causes of TN include multiple sclerosis plaques, intracranial masses, post herpetic neuralgia, and trauma [15]. Neuroimaging, in particular, MRI of the brain with and without contrast, is recommended to rule out any secondary causes. However, many times surgery is required to definitively rule out vascular compression that may not be observed on neuroimaging. Although there are many causes of TN, 90% of cases are caused by compression of the trigeminal nerve root by an artery or vein [13]. Other causes of trigeminal nerve compression include acoustic neuroma, meningioma, aneurysms, or arteriovenous malformation [16]. The compressive effect leads to an axonal injury leading to focal demyelination and subsequently symptoms of trigeminal neuralgia [15]. TN is a clinical diagnosis in which neuroimaging can help differentiate between primary and secondary causes but is not required for diagnosis.

As a direct result of demyelination and neuron hyperexcitability, Lhermitte's phenomenon causes electrical sensation runs down the length of the spine. Although primarily seen in multiple sclerosis patients, other causes of Lhermitte's sign include transverse myelitis, Bechet's disease, and trauma [10]. For these reasons, through history and physical examination must be done to make the diagnosis based on the comprehensive patient presentation. Laboratory testing and imaging have been found to be non-diagnostic in Lhermitte's phenomenon.

Optic neuritis is often the presenting sign of multiple sclerosis [8]. Diagnosis requires clinical suspicion based on the signs and symptoms. Classic symptoms of eye pain with movement and subacute vision loss will trigger ophthalmoscopic examination. In one-third of patients, the optic disc will be swollen, and a poor pupillary response will be elicited with light [17]. MRI will not show optic neuritis;

Table 23.1 Modified Ashworth Scale

Grade	Description
0	No increase in muscle tone
1	Slight increase in muscle tone characterized by catch and release or minimal resistance at the end of the range of motion
1+	Slight increase in muscle tone characterized by catch followed by minimal resistance through the remainder of the range of motion
2	Marked increase in muscle tone throughout most of the range of motion
3	Considerable increase in muscle tone resulting in difficult passive movement
4	Affected region rigid in flexion or extension

however, may be helpful in showing brain lesions implying multiple sclerosis in a patient who may be presenting as new onset multiple sclerosis.

Spasticity is a clinical diagnosis which is determined by physical examination. The differential diagnosis of spasticity includes contractures, rigidity, and catatonia. Several signs that may be indicative of spastic joint include increased muscle tone, muscle spasms, clonus, pain, and postural abnormalities. Severity of spasticity can be graded by a scale, the Modified Ashworth Scale (MAS) (Table 23.1) [18].

This scale is not only important in classifying the severity of spasticity, but also for monitoring the progression of symptoms over time or improvement in symptoms after medical intervention. Additionally, electromyography (EMG) may be used to evaluate nerve conduction studies and guide the diagnosis of spasticity.

23.4 Treatment

Inpatient pain management in multiple sclerosis is guided by the type and severity of pain. This includes non-pharmacologic, pharmacologic, and interventional procedures. Each of these treatment modalities has advantages, disadvantages, and contraindications, which will be discussed.

Non-pharmacological management is often the first-line option for managing mild pain. Initial treatment options consist of non-pharmacological therapies including physical therapy, acupuncture, massage, yoga and meditation, among others [7]. In the acute inpatient rehabilitation setting, patients have physical and occupational therapy sessions which can manage pain in the inpatient setting. However, other non-pharmacologically therapies including acupuncture, massage, yoga, and meditation are often not available in the inpatient setting and will therefore not be further discussed here.

Pharmacological treatment modalities compose the majority of treatment option for inpatient pain management. Pharmacological drugs used include antidepressants, antiepileptics, non-steroidal anti-inflammatory drugs, anti-spasticity agents, opioids, and cannabinoids.

Antidepressant agents include tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors (SNRI) agents, which are the drugs of choice for burning, aching neuropathic pain [19]. Their mechanism of action is inhibiting the presynaptic reuptake of neurotransmitters norepinephrine and serotonin [20]. At low doses, tricyclic antidepressants work for pain. At high doses, tricyclics are effective for antidepressant effects. SNRIs are preferred agents for managing allodynia pain, pain from a stimulus which usually does not cause pain [21]. One randomized, double-blind, placebo-controlled trial studied the effects of duloxetine, a SNRI, on neuropathic pain in patients with MS [22]. In the study, 239 adults were given 60 mg duloxetine or placebo for 6 weeks. Duloxetine-treated patients had a statistically greater mean improvement in average pain intensity than placebo-treated patients [22]. Adverse effects are a large limiting factor to the use of antidepressants for pain management. In a subset of patients, antidepressants may cause nausea, weight gain, sexual dysfunction, insomnia, and dry mouth.

Antiepileptic agents work by decreasing membrane excitability by interacting with other neurotransmitter receptors. Agents used for pain in multiple sclerosis include carbamazepine, pregabalin, and gabapentin. Carbamazepine is an antiepileptic agent inhibiting sodium channels preventing repetitive and sustained action potential firing. Gabapentin binds and inhibits the alpha 2-delta subunit of voltage-gated calcium channels [23]. One study using gabapentin in 22 MS patients showed moderate to excellent pain relief in 15 patients with a daily dose of 600 mg. Notably, 50% of patient's experienced adverse effects of somnolence [24]. Given the sedative effects of gabapentin, it is recommended to dose the medication prior to bed time and up titrate to twice or three times a day as tolerated. Additionally, it is important to consider the patient's glomerular filtration rate and adjust the dose appropriately to prevent gabapentin induced toxicity. Similarly, pregabalin binds the alpha 2-delta subunit and reduces the synaptic release of several neurotransmitters. Adverse effects of antiepileptic agents as a class may cause cognitive impairment, weight gain, dermatological changes, and interfere with hepatic drug metabolism. Importantly, anti-epileptics are teratogenic, increasing the risk of congenital malformations [25].

Topical agents may be used in conjunction to oral medications. One of the most commonly used topical agents is capsaicin. Capsaicin works by depleting substance P levels. Benefits of using capsaicin cream include localized effect with limited systemic adverse effects [26]. The major disadvantage is that capsaicin cream has limited availability in the inpatient setting.

Non-steroidal anti-inflammatory drugs (NSAIDs) are agents preferred for neuromuscular pain. These drugs work by inhibiting the activity of cyclooxygenase enzymes which are responsible for the synthesis of prostaglandins [27]. The most commonly used NSAIDs include ibuprofen, ketorolac and naproxen. These medications are good first-line options for mild to moderate pain in the acute setting. They are available in the inpatient setting and overall have a low cost. One randomized, prospective, double-blind clinical trial compared the efficacy of intramuscular ketorolac versus oral ibuprofen in managing musculoskeletal pain. This study

showed that there was no significant difference in mean pain scores between groups that received ketorolac 60 mg intramuscular with a placebo capsule and groups which received placebo intramuscular injection and ibuprofen 800 mg oral [28]. Prior to initiating NSAID therapy, it is important to consider the gastrointestinal, cardiac, and renal complications associated with this class of medication and should be avoided in certain patients.

Anti-spastic drugs are often preferred in managing spasticity related pain in multiple sclerosis patients. Specifically, oral agents are often desirable due to their easy use; however, they may cause unwanted systemic adverse effects. Therefore, oral agents are typically desired in patients with generalized spasticity. Oral agents can be divided into centrally and peripherally acting agents. Centrally acting agents include baclofen, clonidine, tizanidine, benzodiazepines, and gabapentin. Peripherally acting drugs include dantrolene.

Of oral, centrally acting agents, baclofen is the first-line medication for spasticity management. At the level of the synapse, baclofen works by binding to pre- and postsynaptic gamma aminobutylic acid (GABA) B agonist receptors causing hyperpolarization. This prevents calcium influx and inhibits endogenous excitatory neurotransmitters from being released [13]. Adverse effects to monitor for include drowsiness, excessive muscle relaxation, and hepatotoxicity. Withdrawing from baclofen is associated with severe symptoms including hyperthermia, seizures, and altered mental status [13]. For these reasons, baclofen dosing needs to be carefully managed with gradual tapering.

Alpha-2-agonist agents including clonidine and tizanidine can be used in managing spasticity. These agents inhibit excessive afferent sensory transmission; therefore, decreasing spasticity. However, it is not used as a single agent in managing spasticity due to the adverse effects of hypotension, bradycardia, and drowsiness [13]. Tizanidine is an agent used in conjunction with other anti-spastic agents. Adverse effects of tizanidine include sedation, hypotension, muscle weakness, hallucinations, and prolongation of QT interval [13]. A meta-analysis done to compare the efficacy and tolerability of tizanidine compared to baclofen and diazepam. Two key outcomes were measured: muscle tone and muscle strength. For spasiticy measured by modified ashworth scale, tizanidine was equivalent to baclofen and diazepam. Muscle strength was improved by all three therapies; however, the greatest improvement was with tizanidine [29].

Antiepiletics used in managing spasticity in MS patients include benzodiazepines and gabapentin. Of the benzodiazepine class, diazepam and clonazepam work at postsynaptic GABA A receptors to suppress action of CNS. Both diazepam and clonazepam induce sedation, aiding with sleep by managing spasticity symptoms overnight [13]. Gabapentin is also used as an adjunctive agent. The mechanism of action is thought to be by binding to the alpha 2 delta 1 subunit of calcium channels and inhibiting calcium voltage transmission [13]. Due to its efficacy in managing neuropathic pain, gabapentin is preferred for patients experiencing neuropathic pain and spasticity. Adverse effects of gabapentin include drowsiness, tremors, and nystagmus [13].

Dantrolene is the only peripherally acting anti-spastic agent approved by the US Food and Drug Administration. It works at the muscle by uncoupling excitation and contraction by inhibiting calcium release at the sarcoplasmic reticulum. Adverse effects of dantrolene include liver failure and generalized muscle weakness [13].

In severe cases of pain, non-responsive to other non-pharmacologic and pharmacological therapies, opioids including tramadol, oxycodone, and morphine, may be considered. However, studies have shown that opioids are not as effective and are avoided due to side effect profile. One study, it was found that only a minority of patients with nociceptive pain responded to opioids. Those that experienced >50% pain relief, responded at high doses of morphine. For these reasons, it was concluded that neuropathic pain is poorly responsive to opioids and they are not recommended for routine use for pain in MS patients [30].

There are rising studies to suggest that cannabinoids can be used in suppressing spasticity and pain in multiple sclerosis patients who are refractory to other therapies. Preliminary clinical trials with animal models with multiple sclerosis have suggested strong evidence in reducing spasticity and tremors by mediating CB1 and CB2 cannabinoid receptors [31]. Further research is needed to make more conclusive evidence about the efficacy of cannabinoids in multiple sclerosis symptoms.

After consideration of non-pharmacologic and oral pharmacologic agents, interventional procedures to manage pain in multiple sclerosis patients may be considered. Intrathecal baclofen is one of the most common centrally acting interventions for patients with systemic spasticity. With intrathecal baclofen, the drug is delivered directly to the CNS. This is advantageous due to the ability of highest drug concentration delivery to the CNS; therefore, avoiding systemic side effects [13]. Additionally, with intrathecal baclofen, there is the ability to titrate the level of baclofen intrathecal delivery which can adapt to varied levels of spasticity depending on activity. This therapy is most effective for lower limb spasticity due to the tendency of the highest drug levels at the lower spinal levels. Disadvantages to intrathecal baclofen pump implantation is complications of device placement, pump failure, and overdose. Pump failure can lead to overdose or withdrawal. Overdose can lead to respiratory depression and coma. Baclofen withdrawal can result in hyperthermia, rhabdomyolysis, and disseminated intravascular coagulation [13]. Pump placement complications include risk of infection or cerebrospinal fluid leak.

Injections with botulinum toxin is an intervention largely used for localized spasticity in multiple sclerosis patients. In such patients, focal therapy avoids the systemic symptoms of sedation and generalized weakness. Botulinum toxin works by inhibiting the release of presynaptic acetylcholine at the neuromuscular junction [13]. Additionally, the effects of botulinum toxin are temporary, lasting 3–4 months. Greatest concerns with botulinum toxin injections include dissemination of the toxin to surrounding areas which can cause undesirable effects depending on region affected and muscle weakness. For these reasons, experts should have a strong understanding of anatomy and use electromyography or ultrasound guided to target injections during the procedure [13].

Surgically, neurectomies or rhizotomies may be done for severe pain unresponsive to other pharmacological and interventional therapies. In neurectomies, a peripheral nerve is removed or severed; therefore, reducing transmission of pain signals.

23.5 Pain Assessment Tools

Accessing a patient's pain in the inpatient setting can be challenging due to its subjective nature. When assessing pain, it is important to consider the severity, chronicity, and character of the pain. Additionally, it is important to reevaluate pain regularly using the same pain scale [16].

The verbal rating scale is one pain assessment tool which asks the patient to classify his or her pain with the most appropriate adjective. This can be on a scale of mild, moderate, or severe [16] or no pain at all to extremely intense pain [32]. Benefits of this pain scale include simplicity and easy use. However, due to the limited number of categories, patients may have a difficult time picking which adjective best fits their pain [32].

For patients with limited cognitive ability, visual analogue scores like the Wong-Baker FACES pain rating scale can be used. This scale shows a series of six faces from left to right, a happy face indicating no pain to a crying face expressing most severe pain [16]. Advantages to using the visual analogue scale include rapid ability of a patient to grade pain leading to low patient burden. Additionally, this scale is easily used by a wide age group and those of different socioeconomic and cultural backgrounds. Disadvantages to the visual analogue scale is that it may oversimplify a patient's pain. For these reasons, it is important to use the scale in combination with clinical judgement and evaluation of the patient.

In the numerical rating scale, patients are asked to rate their pain on a scale of 0–10. This pain scale has shown to be effective in that it is easy to use [32].

23.6 Challenges in the Management of Pain While in the Hospital

There are many challenges that arise when managing pain in the inpatient setting. There is the risk of mismanaging a patient's pain. This can lead to physiological and psychological stress to the patient and their families. Physiologically, continuous pain can activate the pituitary-adrenal axis [33]. This can suppress the immune system, leading to increased risk of infections. Within the endocrine system, chronic stress may lead to excess hormone release leading to poor glucose control and catabolism of carbohydrates, proteins, and fat [33]. Additionally, unalleviated pain can activate the sympathetic system leading to adverse effects within the cardiovascular, gastrointestinal, and renal systems. This causes tachycardia, hypertension, and decreased gastric motility therefore increasing the risk of cardiac ischemia and ileus [33]. Psychologically, unrelieved pain may lead to anxiety, hopelessness, and depression.

Of importance, hospital and physician reputations depend on patient satisfaction during their hospital stay. The level of satisfaction has been highly associated with pain relief during their hospitalization [34]. The undertreatment of pain is an important aspect of pain management as opioid epidemic and societal pressure on opioid prescribing has affected physicians.

23.7 Management of Pain in the Inpatient Setting

When deciding on a treatment plan for patients experiencing pain, it is important to consider all treatment options and choose a treatment systematically. First, you must ensure you have the correct diagnosis. In multiple sclerosis, patients have pain stemming from various pathophysiologic pathways which are treated uniquely. Then you must consider the severity, chronicity, and character of the patient's pain. Finally, you must discuss the risks, benefits, and alternatives for each treatment modality proposed. Based on a combined evaluation of pain, a decision on medical management can be used.

Mild musculoskeletal pain should be managed with non-pharmacological interventions including physical therapy. For moderate musculoskeletal pain, non-pharmacological therapies should be used in combination with NSAIDs. For severe musculoskeletal pain, a short term course of opioids may be beneficial, after a trial of non-opioid medications.

For mild to moderate neuropathic pain, topical agents including lidocaine and capsaicin cream should be used. For moderate to severe neuropathic pain, antiepileptic agents including gabapentin may be used.

Spinal infusion therapies are an option for patients with severe multiple sclerosis. Of the FDA approved medications, baclofen is the most commonly used as intrathecal administration. As discussed above, intrathecal baclofen has many procedure-related and medication-related adverse effects. For these reasons, the appropriate candidate must be a patient who has severe symptoms which persist despite having exhausted other non-pharmacologic and pharmacologic treatments. For patients with severe spasticity, a trial of intrathecal baclofen with 50–100 μg should be done. If successful, the patient is deemed a candidate for intrathecal baclofen pump placement [35–37].

In addition to intrathecal baclofen, studies have been done with intrathecal infusion of bupivacaine. One study showed a multiple sclerosis patient with spasticity and pain treated with an intrathecal infusion of 0.5% bupivacaine at 15 mg/L a day. This was increased to 95 mg/L a day after 68 days of treatment and continued for a total of 712 days without any adverse effects [38]. The visual analysis score decreased from 7 to 1 indicating significant improvement in pain.

Intrathecal injections of triamcinolone 40–80 mg have been used as well to manage spasticity and pain. One study showed reduction in spasticity but no support has been shown in managing pain [39, 40]. Another study did a trial of intravenous lidocaine in 30 patients with multiple sclerosis. Achieving a mean plasma level of 2.4 pg/mL, symptoms of Lhermitte's sign, tonic seizures, and neuralgic attacks were significantly reduced [41]. The use of bupivacaine, triamcinolone, and

lidocaine to manage spasticity and pain in multiple sclerosis patients is limited. For these reasons, they are often last resort treatment options.

Patients with multiple sclerosis may present to the emergency department with pain. In this situation, providers must carefully examine patients with a full history and physical examination to determine the type of pain. Key characteristics include acuity vs chronicity, quality, and severity of pain. It is preferred to start with analgesics including NSAIDs and acetaminophen. If pain continues to be inadequately managed, short-acting opioid medications including tramadol, codeine, hydrocodone, oxycodone, and morphine may be used. For severe pain, opioids including fentanyl, morphine, and oxycodone may be used in addition to ketorolac. In states of severe pain, the intravenous route of administration is preferred due to its rapid onset [42]. Due to the potential adverse effects of sedation, respiratory depression, constipation, physical dependence, and tolerance, opioids should be prescribed in the appropriate patient population [24].

Similarly, patients with multiple sclerosis may present peri-operatively and post-operatively for pain management. To ensure appropriate analgesia is provided, providers must consider severity and character of symptoms. Due to the context of the pain, pain may be optimally managed initially with opioids. After immediate post-operative pain subsides, patients should be carefully titrated off of opioid medications to prevent adverse effects including physical dependence.

23.8 Discharge Plan for Pain Management

Follow up after inpatient stay in multiple sclerosis patients is critical. Lack of follow up care can result in worsening of patient's clinical status and risk of inpatient readmission. To ensure a complete discharge plan is in place, provide the patient with a list of medications with administration instructions, list of follow up appointments, and clear instructions on when to seek urgent help. Specifically, follow up appointments should be scheduled with the patient's primary care physician, neurology, and pain management. With a clear and comprehensive discharge plan, effective pain management can be achieved in multiple sclerosis patients after an inpatient stay.

23.9 Summary

- Literature on pain management in multiple sclerosis patients is vastly incomplete due to the reliance of physicians on patient reporting.
- Diagnosis of pain in multiple sclerosis patients should be established with a thorough history and physical examination.
- A multidisciplinary approach combining non-pharmacological and pharmacological therapies should be used to optimize symptom management in multiple sclerosis patients.

- Pharmacological agents should be selected after discussing adverse effects of a drug and alternative options.
- Invasive procedures and surgeries should be considered after patients have tried less invasive, nonpharmacological, pharmacological, and interventional therapies.

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Chapter 24
Patient with Human Immunodeficiency Virus (HIV)

James Romano and Harsh Sachdeva

24.1 Introduction

Our understanding of The Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) has come a long way since its discovery and acceptance by the scientific community in the early 1980s. As of 2017, an estimated 1.1 million people in the United States and 36.9 million people around the globe were living with HIV. Approximately 59% or 21.7 million people were accessing antiretroviral therapy [1, 2]. Early diagnosis and treatment has improved survival rates dramatically. As the result of an aging population living with HIV, we are now seeing the development of many concurrent comorbid conditions such as diabetes, hypertension and obesity. Long term exposure to HIV as well as highly active antiretroviral therapy (HAART) has been implicated in chronic pain symptoms.

Pain has been shown to be present in up to 55–67% of patients living with HIV/AIDS at all phases of disease from seroconversion through to end stage immunodeficiency [3]. The most commonly reported symptoms include degenerative spinal disease, arthralgias and neuropathic pain [4, 5]. The presence of a chronic pain diagnosis was independently associated with an increase in ED visits, radiology procedures and more inpatient admissions indicating stresses on healthcare utilization [4]. Among functional interference measures, sleep was the most commonly identified item along with mood disturbances as well as ability to work [3].

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Peripheral neuropathy is the most common neurological complication of HIV infection. With at least six subsets of peripheral neuropathy, distal symmetric polyneuropathy (DSP) is the most common affecting one third to one half of patients living with HIV. Prior to the widespread use of highly active antiretroviral therapy (HAART), risk factors for HIV-DSP included low CD4 counts and elevated plasma viral load. More recent studies demonstrate that CD4 count and viral load either do not confer additional risk or that higher CD4 count is associated with incidence of DSP [6]. It has been postulated that this trend may represent the longer life expectancy of those living with HIV or that more urgent medical issues in those with lower CD4 counts take precedence over neuropathic symptoms [7]. Other identified risk factors for increased risk of HIV-DSP include patients with a history of substance abuse and advanced age [6].

24.2 Pathophysiology

In order to best understand pain symptoms from HIV, one would be well served to have a good understanding of neuropathic pain. Neuropathic pain has been defined by the International Association for the Study of Pain as "pain caused by a lesion or disease of the somatosensory nervous system." There are a number of damaging stimuli that can manifest as painful neuropathy. We will explore the two primary proposed causes of painful neuropathy in HIV: viral neurotoxicity and antiretroviral therapy toxic neuropathy.

24.2.1 Neuropathic Pain

Basic proposed mechanisms for neuropathic pain can be broken down into the peripheral and central component. Damage to peripheral and central nerve pathways can invoke a number of cellular changes by various mechanisms depending on the source or cause of neuropathy. Sodium channel upregulation as well as other ion channel changes and increases in sympathetic neuropeptides in damaged nerves can promote ectopic or abnormal nerve conduction. Immune response to tissue damage can incur neurogenic inflammation further contributing to neuropathic mechanisms and symptoms. Ephaptic transmission or crossing of sympathetic and nociceptive fibers in the setting of nerve injury has also been suggested although poorly supported at this time. Many central mechanisms to the manifestations of neuropathy have been proposed. The downregulation of inhibitory neurotransmitters (opioid, GABA) and upregulation of excitatory neurotransmitters (ie glutamate) can be a cause or promote disinhibition of pain symptoms. Changes or "Phenotypic switching" of A-beta fiber distributions in the substantia gelatinosa of Rolando (Lamina II) in the spinal cord as a result of peripheral C fiber injury have also been suggested to promote nociceptive transmission from non-nociceptive stimulus [8].

24.2.2 Pathophysiology of Disease, Pain due to Viral Neurotoxicity

Pathologic features consistent with HIV DSP include axonal degeneration of long axons in distal regions, macrophage infiltration and a loss of neurons in the dorsal root ganglion [9, 10]. Loss of cutaneous innervation and reduction in density of epidermal nerve fibers have been shown in seropositive HIV patients [9]. Nerve biopsy specimens vary depending on CD4 lymphocyte counts. Those with lymphocyte counts above 200 cells/mm consistently demonstrated axonal degeneration with perivascular infiltrates whereas those below 200 cells/mm showed mixed demyelination and axonal degeneration with polymorphonuclear infiltrates characteristic of Cytomegalovirus. There have been several proposed mechanisms for virally mediated neurotoxicity either by direct infection of the nervous tissue or by indirect immunomodulatory mechanisms. Infected macrophages release potentially neurotoxic substances such as inflammatory cytokines, chemokines and glutamates. Infected macrophages have also been shown to release proteins such as gp120 which has been linked to cause cell death and "dying back" phenomenon in the dorsal root ganglion (DRG). Cellular metabolic disturbances as a result of mitochondrial dysfunction caused by infection is also possible [10].

24.2.3 Treatment Related Etiology and Pathophysiology

Antiretroviral toxic neuropathy (ATN) can be clinically indistinguishable from DSP in a patient on nucleoside antiretroviral treatment and carries many similar pathologic features [9]. The World Health Organization as of 2016 recommends initiating HIV treatment with two nucleoside reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI). Offending medications have been primarily considered to be the dideoxynucleoside analogues within the NRTI drug class including stavudine (d4T), didanosine (ddI), and zalcitabine (ddC) [11]. Currently, the WHO recommends the discontinuation of stavudine in first-line treatment regimens for tolerability as side effects can be a limiting factor to treatment. Mechanism of neurotoxicity in dideoxynucleoside analogues is thought to be related to mitochondrial toxicity through selective inhibition of gamma DNA polymerase which is important for mitochondrial DNA replication. Pathology studies demonstrate axonal degeneration and extensive loss of unmyelinated nerve fibers [9]. Protease inhibitors such as ritonavir and darunavir have been used in first line treatment regimens in place of a NNRTI. Protease inhibitors may also potentially incur a neurotoxic effect via effects on macrophage derived neurotrophic factors and damage to dorsal root ganglion however, risk associated with drug class remain small in current studies [6].

24.2.4 Central Damage as a Result of HIV

Pathologic alterations in central pathways may be a major factor in peripheral neuropathic symptoms experienced by the patient. Although there are few pathologic investigations of the central nervous system in those afflicted with HIV DSP specifically, spinal cord and central grey matter changes have been reported. The gracile fasciculus, the tract of the spinal cord which provides the conduction pathway for conscious proprioception, vibration sensation, deep touch and visceral pain information to the brainstem undergoes selective degeneration of axons and myelin sheaths in the thoracic and cervical spinal cord [9]. Interestingly, severity of HIV DSP symptoms have been correlated with lower overall cortical grey matter volume [12].

24.3 Diagnosis

Peripheral neuropathy may be the presenting and only manifestation of HIV infection [10]. HIV-DSP as well as antiretroviral treatment toxic neuropathy each share features closely resembling one another such that it can be difficult to clinically differentiate from one another. Symptoms of both include distal symmetric "stocking and glove" pattern numbness, paresthesia, burning sensation and stabbing pain. Given high prevalence of DSP in those living with HIV, exhaustive diagnostic evaluation may not be required. The initial patient encounter should include a focused history of neuropathic pain onset and character, HAART treatment status as well as current regimen. Pertinent social history may help facilitate preventative discussions. Physical exam findings range widely along spectrum of disease. Patients may experience loss of vibration sensation in the great toes, reduction of ankle reflexes bilaterally as well as decrease in pin and temperature sensation in classical stocking and glove distribution [13]. Further diagnostic studies may help confirm diagnosis, document severity or further workup more sinister disease process. Electromyography may show active or chronic denervation patterns with evidence of reinnervation. Nerve conduction studies often show reduction in amplitude or absence of sural nerve sensory potentials [11]. Skin biopsy, which may be helpful in early detection of disease, will show reduction in epidermal nerve fiber density. Skin biopsy studies on HIV patients show reduction in epidermal nerve fiber density prior to onset of neuropathic symptoms. Additional findings suggest that in those with HIV DSP, an inverse correlation to nerve fiber density and pain intensity exists [9].

As previously mentioned, there are many conditions that cause damaging stimuli to the peripheral and central nervous system that may manifest as or cause neuropathy. It is important to maintain a broad differential when evaluating a patient with suspected HIV related neuropathic pain as timely diagnosis with appropriate treatment intervention can potentially stop the progression of or prevent long neuropathic deficit [5, 14]. Inflammatory demyelinating polyradiculopathy has acute and

chronic subtypes, both of which have been known to occur with increased frequency in HIV seropositive people. Motor deficit tends to predominate with relatively minor sensory symptoms. Electrophysiologic studies will be consistent with demyelinating neuropathy with slower conduction, delayed latency and conduction blocks. Spinal fluid protein is often elevated. Treatment involves immunomodulating therapy such as high dose intravenous IgG or plasmapheresis for the acute subtype. Patients with chronic inflammatory demyelinating polyradiculopathy may improve with oral prednisone [5].

Cytomegalovirus related progressive polyradiculopathy is also a feared neuropathic complication in those with advanced stages of immunodeficiency. Distinctive clinical characteristics include a cauda equina syndrome with predominantly asymmetric lower extremity weakness. If the disease goes untreated, flaccid paraplegia, bowel and bladder incontinence may ensue followed by death after just a few weeks. Electrophysiologic studies will show axonal loss in the lumbosacral roots and subsequent denervation in leg muscles. Spinal fluid analysis will be consistent with low glucose, high protein content and polymorphonuclear pleocytosis [5]. Alternative diseases such as diabetes mellitus, vitamin B12 deficiency, hypothyroidism, alcoholism may need to be considered or may very well be coexisting comorbid conditions.

24.4 Treatment

24.4.1 Nonpharmacologic Treatment

Nonpharmacologic treatment of pain symptoms are always an important consideration when discussing pain management strategies with your patients as this may help avoid risks of complications such as side-effects, drug interactions, tolerance and addiction. Preventative medicine discussions regarding smoking cessation, alcohol and illicit drug use are worthwhile. Frequency of reported pain symptoms in those living with HIV has been tied to current tobacco use, former marijuana and former heroin or crack/cocaine use [15]. Although there are mixed reports about the use of alcohol and its relationship to HIV associated pain, in one animal study, rodents exposed to ddC treatment and alcohol did not independently affect nociception, however ddC treatment and alcohol together elicited notable mechanical hyperalgesia in their subjects [16]. At the very least, there have been cited implications on overall quality of life and adherence to treatment in HIV patients that use and or abuse alcohol. Hazardous alcohol consumption may complicate medical management for the disease itself, as well as associated pain symptoms with onset of comorbid conditions such as liver disease [17].

Psychological factors and associations with pain have been investigated in those living with HIV. Several studies have reaffirmed a positive correlation between the presence of psychological distress or illness and pain symptoms [18]. A cohort of

the experience of pain among a group of women with advanced HIV by Richardson et al. noted a significant relationship between pain frequency and depression. As psychological treatments can have a positive impact on many areas of functioning and quality of life, empirically tested therapies should be considered as an important complement to standard interventions [8]. Trafton et al. investigated the implementation of cognitive-behavioral therapy-based pain management in public HIV primary care clinics in which enrollment was associated with significant improvements in pain intensity, function, anxiety, acceptance and overall mental health. Major limitations to the study treatment centered around hardships of attendance as a result of health issues, access to transportation, child/elder care, work conflicts and other competing priorities [18]. Hypnosis is another therapy avenue that has been explored for patients with HIV neuropathy. Dorfman et al. reported significant improvement in reported pain scores, quality of life metrics as well as depression throughout a 7 week follow up period after just a few brief hypnosis interventions in patients living with HIV neuropathic pain. Current results are preliminary and more elaborate study of the possible benefit of hypnosis is warranted [19].

24.4.2 Pharmacological Management

History and physical examination, consideration for associated comorbidities as well as an understanding the pathophysiologic basis for pain symptoms in HIV are key to selecting a pharmacologic regimen for each individual patient. It is important to recognize the possibility of pharmacological interaction with therapy medications when deciding a drug regimen for pain management. The following is a list of common options.

24.4.3 Gabapentin

Anticonvulsants are maintained as a popular treatment option for HIV associated sensory neuropathy. Gabapentin has had notable efficacy in the treatment of various types of neuropathy such as diabetic neuropathy and post herpetic neuralgia. Gabapentin has been suggested to reduce centrally mediated allodynia as well as inhibit ectopic discharge activity from injured nerves [20]. Although the exact mechanism of gabapentin's effect on neuropathic pain remains unclear, the medication exerts effects on alpha2-gamma subunits of L-type voltage gated calcium channels resulting in decreased release of the norepinephrine, substance P and glutamate [8]. A placebo-controlled trial of gabapentin demonstrated that gabapentin was superior to placebo in not only reducing pain but also sleep disturbance associated with HIV sensory neuropathy. Statistically significant adverse effects in the gabapentin group compared to placebo included somnolence (up to 27.4%), dizziness,

ataxia and nausea [20]. Dosage adjustments for those renal dysfunction and advanced age may be necessary.

24.4.4 Lamotrigine

Lamotrigine has been shown to be a well-tolerated and effective for HIV-associated neuropathic pain in patients receiving neurotoxic antiretroviral therapy. Mechanism of action for pain relief may lie in the medication's antiglutamatergic effects by blocking voltage-activated ion channels and stabilizing neuronal membranes. Interestingly, in a randomized placebo controlled trial done in New York, only patients stratified to have been receiving neurotoxic anti-retroviral therapy (ie didanosine, zalcitabine or stavudine) experienced significant improvement of neuropathic pain symptoms over placebo. The magnitude of pain reduction on outcome measures were similar between lamotrigine and placebo in the groups not receiving neurotoxic antiretroviral therapy. Although it is worth noting that the placebo response was comparably larger and more sustained among patients not receiving neurotoxic antiretroviral therapy, this may certainly reflect varying efficacy of pharmacologic interventions as a direct result from the differing mechanisms of nerve injury. Known side effects from lamotrigine therapy range from rash, stevens-johnson syndrome and toxic epidermal necrolysis [21].

24.4.5 Opioids

The use of opioid narcotic medications in treatment has become increasingly controversial as adverse events related to their side effect profile and deleterious consequences of abuse become more apparent. Results and evidence to support opioid use in the treatment of chronic pain in the HIV patient are mixed [22]. With improvements in treatment and care for patients living with HIV, we have seen a transition in the use of opioid prescribing for end-of-life palliative care to long term chronic pain management. Current trends suggest opioids are prescribed at a much higher rate in those living with HIV and at larger doses. This is not without potential for consequence, as it has been suggested that opiates may negatively interact with HAART regimens and impair immune function in unpredictable ways [23]. There are proposed mechanisms that chronic opioid exposure may promote hyperalgesia and exacerbate HIV associated pain [24, 25]. In addition, prescription of opiates among HIV-infected patients has even been linked with increased risk of death [26]. With the availability of other agents (with generally a more acceptable side effect profile) proven to be effective for the treatment of HIV DSP specifically, opioids can be considered as an additive in severe-refractory cases. Patients living with HIV may certainly have development of comorbid conditions or other sources of pain in

which opioids may be potentially beneficial such as osteoarthritis or complications related to opportunistic infection [23].

24.4.6 Topicals

Topicalization has been shown to be potentially beneficial in the treatment of HIV DSP and may be a good option in those unable to tolerate systemic treatments. There has been generally mixed results among varying topical agents, however, capsaicin has had some encouraging evidence for effectiveness. Alterations in nociceptor transient receptor potential vanilloid 1 (TRPV1) have been suggested to play a role in several forms of peripheral neuropathy such as that found in diabetics and post herpetic neuralgia [27, 28]. Capsaicin, a highly selective TRPV1 agonist, activates TRPV1-expressing receptors and produces an initial burning sensation which through repeated exposure can lead to desensitization over time. In a randomized controlled trial of NGX-4010, a capsaicin 8% dermal patch, was administered in a one-time application on subject's lower extremities. After a single 30-min application, trends towards pain improvement were significant in comparison to placebo between 2 and 12 week follow up. Application and use of the capsaicin dermal patch was generally well tolerated among the test groups. Common side effects to the patch ranged from mild to moderate transient application site pain and erythema with more serious adverse events involving infection and infestation [27].

Lidocaine gel has also been shown to have efficacy in treating neuropathy associated with diabetes and post herpetic neuralgia. Well studied, the amide anesthetic lidocaine inhibits nerve cell membrane depolarization by blocking voltage gated sodium channels [8]. So far, only varying results have been reported with respect to pain relief in patients with HIV distal symmetric polyneuropathy. An open label study of 5% topical lidocaine gel by Dorfman D. et al. suggested benefit whereas a randomized controlled trial of its use failed to differ from placebo. Many limitations to the current studies have been discussed including size, patient selection, use of varying pain scales, and poor adherence of gel medications to commonly afflicted areas such as feet and hands. The use of a patch or occlusive dressing over gel applications may ultimately emerge as a superior means of topical treatment [29].

24.4.7 Nerve Growth Factor

Although likely to be of lower yield in the acute inpatient setting, it is worth mentioning the studied use of recombinant human nerve growth factor (rhNGF) for treatment of HIV associated sensory neuropathy. Nerve growth factor (NGF) is

notable for its involvement in stimulating collateral sprouting in damaged peripheral nerves [30]. A multicenter placebo-controlled randomized trial of rhNGF assessed twice weekly self-administered doses compared to placebo over an 18 week period. The treatment group was superior to placebo for the primary outcome measure in median change and reduction of pain scores as well as pin prick sensitivity by the end of the 18 weeks [31]. Benefit was noted to be more pronounced in those with higher baseline pain symptoms. Overall, rhNGF was deemed safe and well tolerated during the trial with injection site pain noted to be the most significant adverse event related to treatment [30]. Although the idea of pathogenesis based treatment leading to repair and revitalization of damaged nervous tissue is promising, much more study in terms of treatment regimen and outcomes are warranted.

24.4.8 Acetyl L-Carnitine

Investigations into the use of acetyl L-carnitine (ALCAR) as a pathogenesis-based treatment in patients with antiretroviral toxic neuropathy have demonstrated possible benefit [6]. ALCAR plays an important role in mitochondrial function and metabolism as well as production of membrane phospholipids. The nutrient may also potentiate the effects of nerve growth factor and promote peripheral nerve regeneration. Although the study size is small, a double blinded, placebo-controlled study of 90 patients concluded that patients receiving ALCAR had significantly reduced mean pain ratings on VAS compared to placebo after just 14 days. Reported adverse events were limited and overall, ALCAR was well tolerated in the study subjects [32].

24.4.9 Cannabis

The controversial topic of medical marijuana continues to be brought to the forefront of news, politics and healthcare. As legality for medical cannabis has seen gradual approval on a state level, more studies and research has become available than ever before. Studies remain conflicting as there has been positive associations with frequency and severity of pain symptoms in HIV patients with respect to marijuana use [15]. A randomized controlled trial done in San Francisco, California investigated smoked cannabis versus cigarette placebo in patients with HIV-associated sensory neuropathy over a 1 week follow up period. Primary outcome measures demonstrated a reduction in chronic neuropathic pain on daily VAS of 34% compared to 17% in the placebo group [22, 33]. There have been conflicting reports among studies as safety is an important consideration with respect to the use of cannabinoids for treatment. Reported adverse events in the study included

sedation, confusion, anxiety and depersonalization. The National Academies of Sciences, Engineering and Medicine (NASEM) concluded that there is substantial evidence for an association between smoking cannabis and respiratory disease, lower birth weight offspring, motor vehicle collisions and schizophrenia or other psychosis [34]. Current literature in side effect profile as well as drug-drug interactions, both short and long-term, leave much to be desired for the cautious evidence-based practitioner.

24.4.10 Neuromodulation

Invasive interventional pain procedures have been employed for the treatment of chronic or intractable pain. The use of implanted spinal cord stimulators (SCS) are becoming popular for treatment of a variety of chronic pain conditions including failed back surgery syndrome, complex regional pain syndrome, traumatic nerve injury post herpetic neuralgia, as well as neuropathy [35]. Although the exact mechanism of pain relief is not certain, Gate Control Theory suggests that pain conduction in small nerve fibers is overridden by stimulation of larger nerves in the transmission pathway. A few case reports are available for SCS use in HIV patients suffering from severe, burning lower extremity pain as well as low back pain and with good results symptoms and function [36]. Although early case reports are promising, sample size demonstrating benefit remains small. Screening and patient selection for SCS implantation remains another important topic that will require further investigation.

24.5 Pain Assessment Tools

Pain assessment tools are of great clinical importance when assessing treatment effectiveness. The Numerical Rating Scale (NRS), Verbal Rating Scale (VRS) and visual analogue scale (VAS) remain some of the most widely used, if not the most widely used measures of pain intensity. VAS is especially popular and has been shown to correlate well with pain associated behaviors. A patient is asked to identify, mark or vocalize a point in a range, often from 0 to 10, the former representing no pain and later the worst pain imaginable [8]. Interventions can be performed, and repeat assessments can be trended over time. Although this can be helpful in the acute setting there are a number of limitations to consider when using pain assessment tools in the hospital. With respect to VAS, as well as many other forms of pain assessment, patient cognitive or sensory motor dysfunction may limit the effectiveness of the tool. Valuable outcome measures, particularly functional recovery, may be undermined or absent altogether which further limits quality of pain assessment tool information [37].

24.6 Challenges in the Management of Pain While in the Hospital

There can be many challenges to effective pain management in the inpatient setting. As many as half of hospitalized patients experience a significant amount of pain during the course of their hospitalization [38]. Pain is frequently underestimated and undertreated in patients living with HIV. In a multicenter study conducted in France, as many as 62% of inpatients reported active pain symptoms and it was estimated that physicians underestimated severity in 52% of patients reporting pain [39]. This isn't without potential consequence, as acute pain that goes untreated carries an increased risk of developing into chronic pain and all of its deleterious effects on function and quality of life down the road. There are many possible perpetrators for poor pain assessment, including misperceptions of pain, misunderstanding that patient symptoms may be related to their disease, and poor physician awareness of HIV and its association with pain to name a few [24, 40]. Pain management may be limited due to treatment necessities, comorbidities, and current pathologic cause for admission. Although widely variable based on geographic location, AIDS related illness and bacterial infections remain the current leading causes for hospital admissions in those living with HIV worldwide [41]. Management of primary disease processes and admission diagnoses may well take priority over addressing painful symptoms. Other inpatient comorbidities such as predisposition to hospital related delirium, poor nutrition, diminished kidney or liver function as a result of admitting disease process all may hinder treatment options.

24.7 Management of Pain in the Inpatient Setting

There are many important considerations when developing an appropriate and effective pain management regimen for patients in the inpatient setting. A high-quality pain management plan should include an evidenced-based, patient-centered, multidisciplinary approach that is efficacious, safe and cost effective [38]. A broad differential should be maintained in the initial evaluation of pain in patients with HIV. Preventative discussions including smoking and alcohol cessation are worthwhile. Non pharmacologic measures should be used under appropriate circumstances and with the proper patient selection. A conscientious approach to pharmacologic management for pain should be employed with respect to patient condition, comorbidities and primary disease treatments. Typical first line medications for pain such as nonsteroidal anti-inflammation and acetaminophen have little benefit in HIV DSP but may be reasonably considered in the setting of multiple comorbidities such as musculoskeletal pain or osteoarthritis. Gabapentin is recommended as a first-line oral medication by the Infectious Diseases of America and is a good starting point when addressing neuropathic pain. Topicals are potentially

beneficial, particularly in patients unable to tolerate systemic treatments. Given the indiscriminate site of action and side effect profile, opioids should not be first line but can be considered as an additive in patients who do not respond to first-line therapies with moderate to severe pain [42]. Plans should be communicated and agreed upon with the patient as well as treatment teams involved.

24.7.1 Acute and Post-operative Pain Management

There are a few important considerations surrounding the perioperative pain management of patients living with HIV. This is especially true as more drug classes and medications are being considered with a multimodal approach to post-operative pain. Although this is certainly not a comprehensive list, many of the common preoperative strategies for intraoperative and postoperative analgesia do not necessarily carry treatment or disease specific contraindications. Premedication with gabapentin, a current mainstay treatment for HIV-DSP, has also been shown to significantly reduce postoperative opioid consumption [43]. Acetaminophen, selective cyclooxygenase-2 inhibitors as well as ketamine have also been shown to reduce opioid consumption and or improve various pain specific outcomes after surgery [44]. Potential drug-drug interaction with respect to HAART is perhaps one of the most important considerations when creating a post-operative or acute pain management plan. Non-Nucleoside reverse transcriptase inhibitors (NNRTIs)as well as protease inhibitors (PIs) may alter common perioperative drug metabolism through induction or inhibition of cytochrome p450 and various CYP-isoenzymes [45–47]. Acetaminophen, metabolized by several CYP enzymes in the liver (1A2, 2E1 and 3D6), should be administered cautiously as it is commonly over-exposed to patients with HIV as well as those with HIV and co-existing liver disease [48]. Non-steroidal anti-inflammatory medications must also be given special considerations in those with HIV, particularly with respect to kidney function. HIVs has been known to be a direct cause of nephropathy and kidney injury. HAART medications such as tenofovir, adefovir and cidofovir have all been attributed to acute tubular necrosis (ATN). Ibuprofen and the selective cyclooxygenase-2 inhibitor celecoxib are metabolized by CYP 2C9 which could be altered in patients treated with HAART. Many opioids such as oxycodone, hydrocodone, fentanyl, sufentanil and methadone all utilize CYP enzymes to some degree for metabolism. Although not intended for analgesia, risk benefit of benzodiazepine use for sedation must also be weighed. Midazolam has been considered contraindicated in combination with ritonavir [44, 49]. Few studies are available, however amide local anesthetics and opioid-containing labor epidural analgesics have been used successfully in patients with HIV without adverse effects or respiratory consequences despite their metabolism via CYP enzymes [50]. It may be prudent to consider the use of various amide local anesthetics for

localization, regional techniques, as well as continuous infusions (ie lidocaine) fors perioperative pain management with respect to their metabolism. Neuraxial techniques such as spinal or epidural anesthesia are viable options in the absence of opportunistic central nervous system infections that may result from immunocompromisation [51].

24.7.2 Discharge Plan for Pain Management

A clearly defined and well s communicated discharge plan can facilitate treatment success, patient satisfaction and reduce healthcare cost and utilization. Quality of discharge planning has been linked to lower rates of 30-day repeat hospitalizations and increase the likelihood that readmissions will be at the same facility [52]. Treatment monitoring should continue by a physician after initiation of a pain management regimen with periodic assessments on pain symptoms, treatment goals, and functioning. Medication adjustments should be allowed appropriate time intervals to take effect. Treatment related side effects and adverse events should also be assessed and addressed appropriately. Specialty care in Pain Management should be made available to patients with complex or refractory pain syndromes. Palliative care consultation may be appropriate to assist with pain management, management of non-pain symptoms and to address the goals of care as indicated [42].

24.8 Summary

- Initial evaluation of the patient with HIV sensory neuropathy is to include a thorough history and physical examination.
- An inventory of the patient's current and previous HIV treatment is important in considering etiology of and treatment of pain symptoms.
- Social behaviors can significantly impact pain symptoms and preventative medicine discussion on smoking cessation, alcohol and illicit substance abuse can be invaluable.
- Non-pharmacologic management options should be discussed and made available to interested patients.
- Pharmacologic management should be considerate to patient functional needs, comorbid conditions as well as possible drug-drug interactions associated with HAART.
- Invasive and surgical interventions should be reserved for severe symptoms refractory to conservative treatment.
- A long-term multidisciplinary patient-centered approach should be employed for treatment and follow up.

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Chapter 25
Patient with an Autoimmune Disease

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25.1 Introduction

Autoimmune diseases have been shown to affect at least 3–5% of given population [1] with certain diseases reaching up to a possible 7–9% of populations based on statistical models [2]. These conditions are usually mediated by an aberrant response of the patient's immune system creating antibodies against one or more organ systems. There is a wide age distribution to these diseases and a slightly higher incidence in women (65%) in general over most disorders [3]. These conditions can be painful in themselves or have treatments/effects that can interfere with the planned treatments of a pain physician. The specific pain generators are diverse among the different disorders but they all have either auto-antibodies or auto-reactive T-cells that lead to the underlying damage caused by the disorder [4].

There have been differing theories of the causes of autoimmune diseases over the years. Recently there has been a greater understanding of the genetic vs environmental factors [1, 4]. There are many different genetic and epigenetic factors that are in play for any given autoimmune disorder. There are many human leukocyte antigen (HLA) associations that have been discovered for these diseases. There is also a role for environmental factors for these disorders including diet, smoking, ultraviolet radiation, infections and other materials that one may come into contact with [1]. There are multiple associations with certain pathogens or other environmental and specific disorders. This knowledge has helped clinicians treating these diseases immensely and will continue to help with treatments and better understanding.

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Of the almost 100 separate autoimmune diseases [1], not all of them can lead to painful symptoms. This chapter will focus on certain more common autoimmune diseases which can lead to painful symptoms, especially in the inpatient setting. A portion of these painful disorders include those that are specific to the organ system targeted, such as autoimmune hepatitis or primary biliary sclerosis. Some of these disorders are due to sequelae of the autoimmune damage (e.g. diabetic neuropathy from Type 1 diabetes). Others are from direct damage to nerves, joints or other tissues from autoantibodies [4]. Certain autoimmune conditions are covered in other chapters in more detail including multiple sclerosis and Guillain Barre Syndrome. While each disease could be a chapter in itself, we will discuss a selection of the most common autoimmune diseases including rheumatoid (RA) arthritis, inflammatory bowel disease (Ulcerative Colitis (UC) and Crohn's disease (CD)), Systemic Lupus Erythematosus (SLE), and idiopathic inflammatory myopathies (polymyositis or dermatomyositis).

25.2 Pathophysiology

The basic pathophysiology is similar for all autoimmune diseases, but the specific mechanisms are different for each disorder. At the core of all autoimmune disorders is the dysregulation of the immune system leading to improper activation of the inflammatory cascade and immune cells [4]. This inappropriate activation of the immune system can lead to pain in a few ways. First, there is direct destruction of tissues by the immune reaction which can lead to somatic pain. It is also thought that the initial injury releases inflammatory factors which then recruit macrophage and T-cells to the corresponding dorsal root ganglion leading to hypersensitization of the nerve bodies [5]. This in turn can lead to proliferation of microglia and astrocytes which further lead to sensitization and feedback leading to chronic pain. This process has been implicated in other models of chronic neuropathic pain and may be applicable to autoimmune diseases.

T cells and microglia are linked with many autoimmune diseases and have been linked to the development of chronic pain in autoimmune diseases. Another mechanism thought to lead to chronic pain in autoimmune disease is the role of autoantibodies. These auto-antibodies can lead to pain through alterations of voltage gated ion channels and through direct structural damage (thought to be the cause in Guillain-Barre syndrome). There are also studies exploring the roles of autoantibodies of pain in diseases such as Sjogren's syndrome, CRPS, and rheumatoid arthritis.

The basic pathophysiology for each of the specific disorders explored in this chapter is as follows:

- Rheumatoid Arthritis: this disease is characterized by activation of the inflammatory pathways leading to synovial cell proliferation. This leads to cartilage destruction and erosions in the bone. This is further exacerbated by pre-inflammatory cytokines such as tumor necrosis factor and interleukin-6 [6]

- Inflammatory bowel disease (IBD): there are both genetic and environmental contributors to inflammatory bowel disease. Genetic components relate to an autophagy pathway that can lead to a modulation of the innate and adaptive immune responses. There are also many environmental effects that can modulate the disease such as smoking, infection, NSAIDs, and vitamin D levels. In terms of immunological response and dysregulation, it is thought that Th1 cells are associated with Crohn's and Th2 cells with ulcerative colitis. It has also been found that polymorphisms of interleukin-23 genes have an association with inflammatory bowel diseases and that this inflammatory molecule has an effect in chronic bowel inflammation. There are alterations in both the innate and adaptive immune systems which lead to the aberrant inflammatory response in the bowel [7].
- SLE: most of the pathology leading to pain is related to inflammation in joints caused by inflammatory cytokines such as interleukin-6, -17, interferon-alpha, tumor necrosis factor alpha and others. Headaches can also occur with autoantibodies reacting with DNA and NMDA receptors, and anti-endothelial/-phospholipid antibodies [8].
- Idiopathic inflammatory myopathies (IIM): these diseases are thought to have both a genetic and environmental component leading to the development of the disease. There are associated HLA haplotypes for different populations with the myopathies. Muscle biopsies show vasculopathy, myopathy with plasma cells, B cells, CD4 cells, and macrophages. There are also complement membrane attack complexes formed from this inflammatory response [9, 10].

25.3 Diagnosis

Diagnosis of each autoimmune disease is specific to certain symptoms and the specific autoantibodies that have been associated with the disease. Diagnostic criteria and laboratory markers have been developed over time and range from non-specific autoimmune tests to specific assays for implicated autoantibodies. This is often done in the outpatient setting since this is where most patients present. We will describe briefly the diagnostic criteria including signs, symptoms and/or laboratory tests.

25.3.1 Rheumatoid Arthritis

These patients present with pain and stiffness in one or more joints (usually in more than one). The wrist, proximal interphalangeal and metacarpophalangeal joints are most often involved. Stiffness of >1 h in the morning is suggestive of the inflammatory process of RA. With active disease, systemic symptoms can occur which include: fatigue, weight loss or fever. The American college of rheumatology updated

diagnostic criteria in 2010. These criteria focuses on patients with clinical synovitis which cannot be better explained by another disease. The patient is scored on the number of joints involved, serology (rheumatoid factor (RF) or anti-citrullinated protein antibody (ACPA)), acute phase reactants (erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)) and duration of symptoms [6].

Laboratory tests that are obtained include RF and anti-CPA. RF is not specific while anti-CPA is more specific. These patients often have a positive anti-nuclear antibody test as well. In the acute phase, ESR and CRP can be useful to follow progression and treatment of RA [6, 11].

25.3.2 Inflammatory Bowel Diseases

Both Ulcerative Colitis and Crohn's disease often present as undifferentiated diarrhea, abdominal pain/cramping and hematochezia. History, physical exam, laboratory studies and finally endoscopic collection of biopsies are needed to come to the diagnosis of inflammatory bowel disease. Important questions for history center on ruling out other diseases (such as infection, ischemic disease, radiation) and a thorough family history. There are other signs such as anemia, osteoporosis, calcium oxalate kidney stones, gallstones, oral lesions, and concurrent autoimmune diseases associated with inflammatory bowel disease. Physical exam can show abdominal tenderness and rectal exam can show perianal skin problems associated with Crohn's disease [11].

Though endoscopy is the gold standard, other tests such as elevated fecal calprotectin and stool lactoferrin can be helpful in the diagnosis. Certain antibodies such as anti-saccharomyces cerevisiae, anti-escherichia coli outer membrane porin and perinuclear antineutrophilic cytoplasmic antibody can be helpful. None of these are the most sensitive but as a panel can reach levels of reasonable sensitivity and specificity [11, 12].

Endoscopic examination and a tissue biopsy continue to be the gold standard in the diagnosis of IBD and the differentiation between Crohn's disease and Ulcerative colitis. Ulcerative colitis is seen beginning at the rectum and continuing to a proximal portion of the colon and has a clear stopping point. Biopsy findings will only show mucosal and submucosal changes, unlike in Crohn's disease. Crohn's disease can be seen in any or all of the GI tract. IBD with inflammatory changes found outside the colon is diagnosed as Crohn's disease. There are patchy and non-continuous lesions or ulcerations found in Crohn's disease. Biopsies for Crohn's disease will show transmural inflammation and non-caseating granulomas [11, 12].

25.3.3 SLE

SLE affects multiple organ systems and there have been multiple revisions to the original criteria developed in 1971 created by the American College of Rheumatology. The most recent revisions were created and validated in 2012 by

the systemic lupus international collaborating clinics [13]. Each of the criteria had items in six different categories including: cutaneous manifestations, joints, serositis, renal disorder, hematologic disorder, and immunological abnormalities. The patient was required to satisfy four or more of the criteria for a diagnosis. The most recent criteria require at least one clinical and one immunologic item for the diagnosis.

The 2012 items are listed below with their categories [13].

- Cutaneous manifestation: acute, subacute or chronic cutaneous lupus erythematosus, oral ulcers, non-scarring alopecia
- Joints—synovitis in more than two peripheral joints with pain, tenderness/swelling and morning stiffness
- Serositis—pleuritis, pleurisy, pleural effusion, pericarditis, pericardial effusion
- Renal disorder—urine protein creatinine ratio increased or >0.5 g of protein in 24 h, or red blood cell casts
- Hematologic—hemolytic anemia, leukopenia, thrombocytopenia
- Immunologic—positive ANA, positive anti-dsDNA, Anti-Sm, antiphospholipid antibody, low complement (C3, C4, CH50), direct coombs test in the absence of hemolytic anemia

The overall goal is to diagnose this heterogeneous disease with as much confidence as possible to properly treat these patients.

25.3.4 Idiopathic Inflammatory Myopathies

The diagnosis of dermatomyositis and polymyositis starts with a thorough history and physical. Some signs in the history include proximal weakness and/or myalgias. Physical exam findings include skin findings (Gottron's papules or heliotrope rash), weakness on neuromuscular exam, and a careful examination of the joints. Laboratory findings usually include elevated muscle enzymes such as creatine kinase or aldolase. Immunological testing includes an anti-nuclear antibody panel with special attention to anti-Jo-1 (myositis specific and an anti-synthetase) and antibodies against Mi2, SRP, PM/Scl and Ku [9].

More invasive testing is sometimes needed for a diagnosis and differentiation. These can include EMG, MRI, or biopsy. Muscle biopsy can be used to differentiate between polymyositis and dermatomyositis if skin manifestations are not clear. In dermatomyositis, there is injury to capillaries and perifascicular fibers with mostly CD4+ T cells. In polymyositis, there is damage in the fascicle and individual myofibers show infiltration of CD8+ T cells. There is no vascular destruction found. EMG can also be used to assist in diagnosis to rule out neurological causes. EMG can show increased membrane irritability with increased spontaneous fibrillations, low amplitude, and short duration polyphasic motor unit potential and complex discharges. MRI or ultrasound can also be used to look for myopathic changes in the muscles [9, 14].

25.4 Treatment

Pain management in autoimmune diseases is often targeted at reducing the underlying inflammation of the diseases in addition to treating pain as a symptom. There are many immunomodulatory medications (both biologic and nonbiologic) that have been developed or are in development for the treatment of autoimmune diseases. These can often be complementary to traditional pain management medications and techniques. In the hospital, traditional pain management techniques may need to be modified based on the patient's baseline anti-inflammatory regimen. Patients in the hospital may be presenting with worsening disease (flares) or pain from another condition which needs to be managed. In both these scenarios, the patient's baseline treatment regimen needs to be taken into account when recommending or initiating treatments. Finally, for patients refractory to all other treatments, IVIG or plasmapheresis may be necessary to decrease the amount of circulating autoantibodies.

General non-pharmacologic and pharmacologic strategies for pain management also apply to pain management for auto-immune disorders whether in or out of the hospital. For patients with inflammatory arthritis or generalized pain, movement and physical therapy is important and can help with joint mobility and decrease pain/stiffness over time.

25.4.1 Rheumatoid Arthritis

Treatment for RA generally revolves around reducing joint swelling and pain, preventing damage to bone and helping to sustain a quality of life. The main treatments are called disease-modifying antirheumatic drugs (DMARDs) and are designed to block cytokines in the inflammatory cascade that leads to the destructive inflammation of RA. Methotrexate is the first line therapy but may be contraindicated or poorly tolerated due to side effects (including liver damage, ulcers, hair loss, teratogenesis). Other non biologic medications include hydroxychloroquine or sulfasalazine which are used for patients with milder disease. The main class of biologic agents are anti-tumor necrosis factor alpha (TNF) monoclonal antibodies. These include adalimumab (Humira), etanercept (Enbrel), infliximab (Remicade), and others. Adverse effects of these medications include activation of latent TB or opportunistic infections. These can be used in conjunction with non-biologics and have been found to be more effective than monotherapy but can have increased adverse effects. Other mainstays of treatment include oral corticosteroids and NSAIDs. These are recommended to be for short courses of treatment as they can have significant side effects [6].

Non-pharmacologic treatment of RA has not been well studied but there are certain activities and interventions that seem to work to help reduce pain and improve quality of life. Exercise has been shown to be beneficial for these patients and not deleterious. Other disciplines such as tai chi and yoga are being studied and

early studies have shown effectiveness [6, 10]. Studies exploring dietary changes (e.g. Mediterranean diet) have not shown evidence of benefitting nor did studies of acupuncture [10].

For patients with RA in the hospital, joint pain is likely the most common cause of pain. For flares of disease from RA itself, high dose immunosuppressants will likely be necessary. Flares do not necessarily necessitate hospitalization, but potentially could and helping in those flares can improve patient outcomes [15]. Pain management recommendations can include standard pharmacologic interventions including oral adjuvants and oral opioids in certain cases.

There continues to be advancing research in this field. Traditionally, there hasn't been much benefit for neuromodulation for rheumatoid arthritis. One group has shown that dorsal root ganglion stimulation may show improvement in pain symptoms as well as inflammation itself in animal models. Pan et al. showed in a rat model of RA that stimulation of the dorsal root ganglion could lead to normalization of affected limbs [16]. They found that ganglionic field stimulation in the rat model helped to decrease neurogenic inflammation in this rat model and could be promising in future studies. Another field of research that is emerging is vagal stimulation for reduction of inflammation. Vagal stimulation has been found to inhibit TNF production in macrophages. This may be useful in the future as a treatment but is still in animal models [17].

25.4.2 Inflammatory Bowel Disease

The treatment for IBD varies slightly for UC or Crohn's disease but both focusing on alleviating inflammation along the digestive tract. Treatments are broken down into induction and maintenance therapies. Diet and bowel rest can also play a big role in flares or general management of IBD.

For patients with ulcerative colitis, the choice of treatment depends on the severity of the disease. For milder diseases, aminosalicylates (sulfasalazine or 5-aminosalicylate) are the treatment of choice. These can be administered topically or orally depending on the extent of the disease. For more severe disease, high dose steroids oral or IV (depending on the severity) may be needed for treatment and symptom control. This treatment can be refractory in upto 16% of cases and monoclonal antibody therapy may be necessary. These include infliximab, adalimumab, and golimumab. Cyclosporine can be used, but does have more side effects and often is not tolerated. For maintenance therapy, aminosalicylates or azathioprine are effective [11].

For patients with Crohn's disease, a somewhat different approach has been found to be best. Topical agents are less useful due to the wider spread of the disease. Aminosalicylates are commonly used but evidence is not strong for their use. Oral Budesonide has been found to be useful and more effective than aminosalicylates or prednisone with less side effects for mild or moderate disease. For moderate to severe disease, azathioprine or methotrexate and be used in combination with short

courses of higher dose steroids. Biologic agents such as Infliximab (or adalimumab and certolizumab) can be effective as well if there are contraindications to steroids. Studies have shown that azathioprine plus Infliximab as a combination are more effective than either one separately. For maintenance, azathioprine or methotrexate or biologic agents have been shown to be helpful, especially for reducing the need for steroids [11].

For patients in the hospital, there can be many challenges. For ulcerative colitis, patients are already likely on anti-inflammatory medications and NSAIDs would likely be contraindicated. For severe cases of ulcerative colitis, there is an increased risk of toxic megacolon [11]. This risk can be further increased with the use of opioid, anticholinergic or antidiarrheal medications among other interventions. If the patient is refractory to medical treatment, surgical consultation for more definitive treatment may be required [11, 12].

There have been some small observational studies into interventions that may reduce inflammation for IBD patients. Liu et al. looked at stellate ganglion blocks to decrease inflammatory cytokines in trauma patients. They found a decrease in pro-inflammatory cytokines which may help to decrease inflammation and could potentially be translated into treatments for inflammation for autoimmune disorders [18]. Zhao et al. looked at 120 ulcerative colitis patients who were randomized into groups that received sulfasalazine (control) and a series of stellate ganglion blocks. They found that the experimental group had better pain control and similar disease resolution on colonoscopy [19]. This is a small study but could point to treatments in the future for refractory pain in these patients. Finally, some alternative therapies have been found to be effective. Changes in diet, antibiotics, loperamide and nicotine transdermal patches have been found to help with abdominal pain in studies. Psychological treatment including stress management and CBT were found to be effective [20].

25.4.3 SLE

Most of the painful symptoms from lupus come from joint inflammation but there are some that have a secondary fibromyalgia type pain. As with other autoimmune diseases, the mainstay is treating inflammation. For some milder cases, non-steroidal anti-inflammatory drugs can be used. In more severe cases, steroids and immunosuppressive therapy are required. Certain biologics such as belimumab or abatacept have been shown to be effective [21].

Most pain from SLE can be treated in a stepwise fashion similar to many other pain syndromes. Treatment starting with conservative measures and working with other adjunctive analgesics and possibly tramadol. A special consideration for pain in lupus or other inflammatory arthritis can be avascular necrosis of large joints mainly from high dose steroid use. Pain control for AVN requires multimodal analgesics up to and including opioids. Definitive management is usually total joint replacement which is postponed as long as possible [21, 22]. Those with widespread pain syndrome often need multispecialty treatment including psychological

treatment including coping mechanism training and well as aerobic exercise [8]. Medications such as NSAIDs, acetaminophen, and gabapentin or pregabalin can be helpful in treating this type of pain [8].

25.4.4 Inflammatory Myopathies

As with the other autoimmune diseases, the mainstay of treatment is immunomodulatory treatment with a variety of medications. There is very little data for treatment for myositis but there are some treatment options available. Mild disease can be managed by systemic analgesics for pain. Moderate or severe disease requires immunomodulatory treatment. Aggressive treatment is recommended in the acute setting with high dose oral steroids or azathioprine/methotrexate [8, 23].

Flares in the hospital are likely rare with this disease, but they may occur. The strategy should be the same as the other autoimmune/inflammatory diseases. Higher dose immunosuppressants/immunomodulators are likely to be used along with standard pain management regimens.

25.4.5 Treatment in Special Situations

There are a few situation in the inpatient setting that are specialized for the pain physician. These can include perioperative or trauma care as prime examples. For patients with autoimmune diseases, the care in these areas do not deviate from standard of care too much, but there are some challenges.

For perioperative care, patients are often taken off their DMARDs (mainly biologics) as these can hinder proper post-operative heading and increase risk of infection. This may lead to flares in the disease and flares in pain [24] but is much less of a risk than the other complications of staying on the biologics. There do not appear to be any specific contraindications for regional anesthesia, but certain sequelae of the disease may preclude the use of neuraxial anesthetics. Patients with SLE can present with thrombocytopenia which may preclude the use of neuraxial anesthesia [13]. Overall, standard of care treatment is reasonable for these patients and they might benefit from regional anesthesia if appropriate for the specific surgical case due to the increased chance of flare of their disease and pain.

For patients with autoimmune diseases after trauma, there is little data available for changes in treatment patterns. There is a theoretical chance of a flare of the pain due to a flare in disease from the increased inflammation due to trauma. Regional techniques including nerve blocks or neuraxial techniques may be helpful in this situation, especially if there are flares. Medication management as previously described can also be helpful for these patients. Use of non-opioid medications can aid in the management of pain but opioids can also be used if other measures fail to control the pain.

It is very important to check organ functions as autoimmune disease have systemic effects on many organs including the kidney and the liver among other organs. The metabolism and excretion of medications may be impaired by the disease and careful dosing will be required.

25.4.6 Challenges in the Management of Pain While in the Hospital

There are many challenges to the management of patients with pain from autoimmune diseases while hospitalized. Some patients can be hospitalized for worsening pain due to their disease. Those that have pain from other sources may have complications in the treatment plan due to the medications they are taking to modify their underlying autoimmune disorder.

The treatment for patients that are having a flare in their pain/disease can vary greatly. For most of the autoimmune disorders, these flares are treated with potent anti-inflammatory medications such as high dose steroids or immunomodulatory medications such as anti-TNF alpha monoclonal antibodies or other immunosuppressants (e.g. methotrexate). Many of these medications can have side effects that make it more difficult to use the more common pain medications or interventions. Steroid injections, whether neuraxial or in major/minor joints, may be limited due to the high dose oral steroids these patients can be on in the hospital. Many of these patients may be started on immunomodulatory or immunosuppressive agents which predisposes the patients to infection. Patients undergoing procedures for pain will need to be especially screened for infection and sterile procedure is very important for these patients.

Another challenge involves the outpatient use of opioids in patients with autoimmune diseases for their chronic pain. Even though there is limited evidence for long term opioid use, there are many patients with painful autoimmune disease who are on chronic opioid medications. Zamora-Legoff et al. looked at a retrospective sample of 501 patients with RA vs 537 without RA and compared the rate of opioid use between these two groups. They found a much higher use of opioids in the RA group and that up to a third will be prescribed an opioid and 10% are on chronic opioid therapy [25]. Summers et al. looked at 462 patients with SLE and found that 31% of the studied patients used prescription opioid medications compared to 8% of patients without SLE [26]. For patients with inflammatory bowel disease, chronic opioid use has been shown to lead to higher odds of emergent encounters and higher costs [27]. This study by Alley et al. looked at retrospective data from 76,171 patients from the Truven Health MarketScan database in regard to emergency visits. Though this trend is changing slowly, there will still be many patients in the hospital on chronic opioid therapy with autoimmune diseases. For these patients, it is necessary to factor in their opioid tolerance and baseline opioid dose when recommending a plan for pain control. It is important for the pain provider to follow up with the

patient's outpatient provider if there are any changes in the patient's opioid regimen to provide a smooth transition from the hospital setting.

Much of the treatment for hospitalization for worsening disease is likely to be directed by rheumatologists with changes in DMARDs and other immunosuppressants or immunomodulators. It is key to communicate with these providers about any changes in other more traditional pain medications in order to minimize interactions. A pain management specialist can help with recommendations for concurrent therapies and guidance for post-hospitalization care.

25.5 Pain Assessment Tools

There are many pain assessment tools for chronic pain both in the hospital and as an outpatient. These are well described in other chapters of this book and many pertain to autoimmune diseases. Chronic pain is a complex disorder with biological and psychosocial components. To properly assess pain, multiple components need to be taken into account. First, intensity can be measured with the visual analog scale or numerical rating system. These can be somewhat reliable, but they do have drawbacks, as the answers can be highly subjective [28, 29]. Pain quality is also important as this can help further qualify pain and guide treatment. This can be measured by the McGill pain questionnaire. Other measures and questionnaires are available to measure the psychosocial aspects of pain too. Finally, there are assessments designed to look at the effects of pain on daily activities. Some of these include the more general pain disability index and more specific assessments such as the Western Ontario MacMaster Osteoarthritis Scale or the Roland-Morris Back Pain Disability Index [28]. These can help to gauge the effects that pain has on daily life and to help guide treatment over the short and long term.

25.6 Discharge Plan for Pain Management

Any discharge plan for patients in the hospital requires close communication with the patient's primary care provider and other providers. For these patients, it is key to collaborate with their rheumatologist or gastroenterologist (in the case of IBD) to assess anti-inflammatory treatment. It is necessary to determine who will follow up with the plan after the hospitalization. This may include their primary care physician for minor changes in their pain plan. They should follow up with a rheumatologist if any anti-inflammatory treatments were altered or initiated. Finally, if there is a complex pain management plan including interventions or complex medication management, the patient may benefit from following up with a pain management specialist after discharge from the hospital.

For new anti-inflammatory regimens, there may be tests that need to be completed and followed up on because of the adverse effects of some of these medications. Most biologic agents have the risk of TB activation and screening is recommended for patients starting on these medications. Patients who are at risk for infection or have hepatitis infections should be screened and followed carefully. Those at risk for activation of hepatitis may benefit from antiviral therapy and should follow up with the appropriate provider [10].

25.7 Summary

- Appropriate recognition and diagnosis of the specific autoimmune disorder in patients in the hospital can be helpful in guiding treatment of pain in the hospital.
- It is important for the pain management practitioner to communicate with the patient's rheumatologist or practitioner who is treating the disease and assess the patient's current treatment plan including medications and adjunctive therapies.
- Treatment of the different autoimmune disorders is targeted at the inflammatory cascade with immunosuppressive medications such as steroids or immunomodulatory agents such as anti-TNF monoclonal antibodies.
- Basic pain management strategies and medications can be helpful as an additional part of the pain relief plan.
- Normal medications such as NSAIDs or interventions such as steroid injections may be contraindicated based on the patient's baseline anti-inflammatory treatment course (including high dose steroids, aminosalicylates or other immunosuppressive medications).
- It is important to keep in mind any immunosuppressive medication the patient is on when performing a procedure as their infection risk will be increased.
- New medications and procedures are being investigated and show some possible promise in alleviating pain for the patient with autoimmune diseases.
- Check labs to determine any kidney or liver disease which can impact metabolism and excretion of different medications.

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Chapter 26
Patient with Guillain Barre Syndrome (GBS)

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26.1 Introduction

The disease classification known as Guillain-Barré Syndrome (GBS) represents an assortment of immune-mediated polyradicular neuropathies, all of which feature the inflammatory demyelination of peripheral nerve tissue [1]. The eponymous title of this group of related conditions recognizes the French neurologists Georges Guillain and Jean-Alexandre Barré, who along with André Strohl described the con-

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dition in 1916. While it was initially considered a single, discrete disease entity, more contemporary assessments have led to the subcategorization of GBS into multiple disease variants according to their unique histological features and immunopathologies [2]. Nevertheless, the various disease subtypes grouped under the GBS heading all display similarities in their pattern of symptom onset, tempo, and evolution of disease. Moreover, the subtypes also share in common a distinctive association between the onset of the syndrome with a preceding infectious event—a well-known hallmark of GBS.

In the post-polio era (1990s onward), GBS represents the most common cause of acute neuromuscular paralysis worldwide [3]. However, it is nevertheless still an uncommon condition, occurring with an incidence of less than two cases per 100,000 depending on the study at hand. While the disease is not specific to any age group, its frequency is generally higher among adults than in children and affects 50% more men than woman. Yet, despite the low overall disease burden, the aggregate costs attributable to the illness in monetary terms are substantial, as the current treatment options available are cost-intensive, and patients often require extended hospital stays and treatment protocols. In the US, the estimated annual costs of GBS reached $1.7 billion [4].

In general, GBS presents sporadically and in an acute fashion, typically within 4 weeks following a benign infection, usually involving the respiratory or gastrointestinal tract [5]. While the precise etiology is still incompletely understood, this antecedent infection is thought to serve as the triggering event, with the ensuing autoimmunity occurring as a consequence of epitope cross-reactivity between host and microbe antigens. This phenomenon is referred to as “molecular mimicry”, and it manifests as an acute polyneuropathy because the targeted host antigens serve as components of myelinated peripheral nerves. The most contemporary understanding of this mechanism is described in further detail in the ensuring sections.

The initial presentation of GBS is most commonly associated with motor symptomology. Specifically, ascending, symmetrical, “stocking glove” weakness is a cardinal feature. However, sensory features, including pain, are also extremely common. In fact, pain has been reported to occur in anywhere from two thirds to nearly 90% of cases, and may, in fact, be the presenting symptom of the condition in many cases [6]. The mechanisms accounting for the pain associated with GBS is heterogeneous and can be both neuropathic and nociceptive in nature. The manner in which pain presents is highly variable and nonspecific. It may range from mild to severe and can occur in the acute and chronic settings. For healthcare providers involved in pain management, familiarity with the various presentations of pain symptoms in patients with GBS is important, as they may be severe in quality and can be frustratingly difficult to treat. Not surprisingly, current evidence suggests that pain is often not adequately treated in this patient population. Considering the complexity of the disease as well as the manner of pain associated with it, achieving adequate symptom control is difficult and is in need of greater inquiry. This point is illustrated by the results of a 2015 Cochrane review, which concluded that only

weak evidence currently exists to support pharmacologic interventions for pain control in GBS.

Since its discovery in early in the early 1900s, the mid and late twentieth century witnessed great progress in characterizing the pathological basis and clinical aspects of the disease [7]. Major areas of progress since the turn of the century involve more precise understandings of the immune-base etiology of the disease, greater delineation of the various different possible presentations, and advancements in diagnostic and prognostic modalities [3, 8]. In addition, management of the disease process itself has seen considerable progress over the past few decades with the application of treatments such as plasmapheresis and the advent of novel immune-based strategies like intravenous immunoglobulin G (IVIG) infusion. However, the supportive management of patients and their pain during the course of the disease remains an important and challenging component of the approach to patients with GBS. To this end, there remains a continued need for large, high quality studies to better evaluate the putative therapeutics for pain management.

26.2 Pathophysiology

While the exact pathophysiology of GBS has never been fully described, the syndrome causes paralysis through a post-infectious auto-immune response that attacks the myelin sheath(s) surrounding peripheral nerve axons (Fig. 26.1). GBS has many different clinical subtypes/variants. These subtypes are used to describe both the

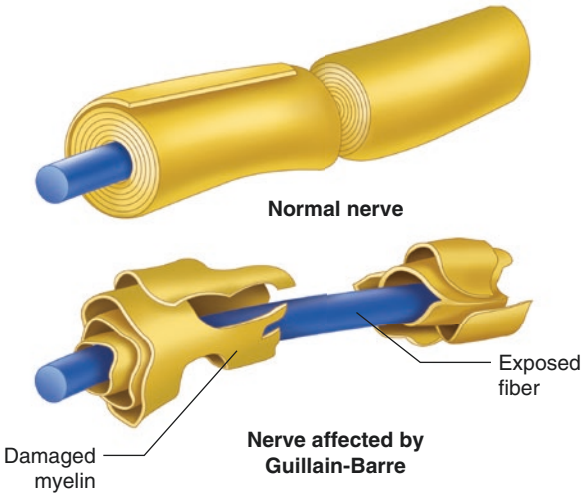

Fig. 26.1 Changes in nerve fibers in Guillain Barre Syndrome

severity and the distribution of the disease process. The most common GBS subtypes are listed and briefly described below in order from most common to least common:

- Acute Inflammatory Demyelinating Polyneuropathy (AIDP): a gradual and symmetric paralysis coinciding with areflexia (lose of deep tendon reflexes) that progresses over 2–4 weeks before beginning to ameliorate.
- Miller Fisher Syndrome (MFS): paralysis—specifically affecting the lower limbs and the eye muscles, and areflexia of the affected muscle group(s)
- Acute Motor Axonal Neuropathy (AMAN): similar to AIDP, AMAN results in a gradual and symmetric paralysis coinciding with areflexia (lose of deep tendon reflexes), but in AMAN the nodes of Ranvier are the initial sites of immune system attack. Clinically AMAN has a quicker clinical course, with the worst symptoms developing within days of onset.
- Acute Motor and Sensory Axonal Neuropathy (AMSAN): is similar to AMAN and AIDP, but in this variant the nodes of Ranvier of sensory nerves are also attacked. The clinical timeline is the same and AMAN.

The four clinical variants described above comprise more than 95% of all GBS cases worldwide. An exhaustive discussion of all GBS variants is beyond the scope of this paper [9, 10]. GBS can occur sporadically, or in clustered. Over the past 25 years, the incidence of GBS has remained stable at 1–4:100,000. 2–3% of all cases of GBS are fatal, most fatal cases of GBS involve respiratory failure. While patients of any age can be afflicted by this syndrome, GBS is less common in the pediatric population and in those over 80 years of age. There is a slight male predominance in incidence. Until the early 1990s, there appeared to be no differences in how the disease process expressed itself in different racial and ethnics group. Since 1993, population studies have shown that the AMAN and AMSAN variants are more prevalent in China and Japan. The AIDP variant is the most common worldwide and is even more prevalent in the United States and Europe. Caucasian individuals in the United States are 1.5–1.6 times more likely to be affected by GBS than African Americans.

The largest known cohort/"epidemic" of GBS occurred in the United States in 1976. That year public health officials became concerned that a swine influenza strain would be particularly lethal, and a massive effort was made to vaccinate the American population. An unintended consequence of this vaccination effort was a spike in the numbers of cases of GBS. The relative risk for developing GBS after having been administered the 1976 swine influenza immunization was 6.2. Of the people who received the swine flu vaccine more than 1100 developed GBS. While some clinical courses were limited to limb weakness, the majority of patients went to develop respiratory symptoms during the 6–8 week post-vaccination clinical course [11].

There are no rigidly defined risk factors for GBS, but over the past 50–60 years several associations have been observed. Development of GBS is more common after respiratory and GI illnesses—as compared to infections affecting other organ systems. The most common antecedent infections to GBS are caused by *Campylobacter jejuni (C jejuni)* and cytomegalovirus. Other infectious agents that

are associated with GBS include (but is not limited to): mononucleosis, parainfluenza, rubeola (measles), mumps (rubulavirus), Hepatitis A, Hepatitis B, Hepatitis E, *Mycoplasma pneumoniae* (*M. pneumoniae*), salmonella, chlamydia, swine influenza (see above), human herpes virus, Human immunodeficiency virus, and Zika virus. Certain vaccines have also been connected to GBS. There was a statistically significant decrease in GBS cases when the rabies vaccine stopped being cultured in nervous system tissues. It is still debated whether or not live vaccines have a stronger association with development of GBS compared to inactive vaccines.

Over the past 30 years, the medical community has come to accept that GBS is a post-infectious auto-immune mediated process. Both the cellular and humoral arms of the immune system play important parts in the disease process. To understand this further, consider the hypothesized connection between AMAN, AMSAN, and *C jejuni*. During the enteritis caused by *C jejuni*, human IgG antibodies recognize and attack the lipopolysaccharide molecule on the capsule of the bacterium. The subsequent immune response clears the infection from the body. Unfortunately, certain myelin glycolipids have a similar molecular footprint to the *C jejuni*'s capsule lipopolysaccharide. The high-titer of IgG antibodies that develop during the *C jejuni* infection can cross-react with the myelin glycolipids found on the myelin sheaths surrounding nerve axons. The misidentification of the myelin glycolipids by the body's antibodies then triggers lymphocytes and macrophages to attack the myelin surrounding the axons. As the myelin sheaths are destroyed nerve conduction is lost and paralysis develops clinically. Macrophage and lymphocyte attacks of myelin are well documented in electron microscopy of nerves of GBS victims. In addition, declining IgG titers in GBS patients parallels clinical improvement. In non-lethal cases of GBS, nerve biopsies in recovering patients have shown myelin regeneration around intact axons. While the association between AMAN, AMSAN, and *C jejuni* seems clear cut, AMAN and AMSAN are not the most common variants of GBS. AIDP is the most common GBS variant, and no consistent immunopathogenic model has been established in the majority of AIDP cases. While significant advances have been made, medical scientists are still researching the exact molecular pathogenesis of all the different GBS variants [9, 10, 12].

26.3 Diagnosis

Early diagnosis of GBS can be complex in clinical practice due to its variable presentation and different clinical subtypes.

Required features

- Progressive bilateral ascending flaccid weakness of proximal and distal muscles of upper and lower extremities and may vary from mild paresis to complete paralysis. Patients usually present early in the course of the disease within a few days to weeks after symptom onset
- Areflexia/hyporeflexia in affected arms and legs

Supportive features

- History of antecedent respiratory, gastrointestinal infections and viral infections, vaccination, surgery or trauma
- Acute onset, fulminating monophasic disease course which initially progresses rapidly followed by clinical plateau and recovery [13]
- Mostly symmetric pattern of limb weakness and involvement of motor cranial nerves (VII, XII, X, III, IV, VI and XI). Patients can present with bilateral facial nerve palsies, oculomotor weakness, oropharyngeal weakness, dysphagia or speech disturbances
- Paresthesia in the hands and feet in more than 80% of patients [14] but often minimal sensory signs
- Dysautonomia-diarrhea/constipation, bradycardia, tachycardia, cardiac arrhythmias, blood pressure lability, reversible cardiomyopathy, hyponatremia, Horner's syndrome [14]
- Positive findings in Electromyography, nerve conduction studies and cerebrospinal fluid analysis

Other clinical features

- Neck flexion weakness and respiratory failure requiring ventilatory support
- Back pain or pain in the extremities
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH), due to autonomic involvement
- Excluding alternate diagnostic conditions which can cause neuromuscular weakness

Findings that should create doubt about possibility of GBS diagnosis

- Persistent asymmetry of weakness
- Severe pulmonary dysfunction with limited limb weakness at onset
- Predominant sensory signs with no weakness at onset
- Bladder or bowel dysfunction at onset
- A well demarcated sensory level on neurological examination
- Fever at onset or increase in white cell count in cerebrospinal fluid >50/μL

Clinical Subtypes of GBS

1. Classic GBS: acute immune mediated inflammatory demyelinating polyradiculoneuropathy (AIDP) is the most common form characterized by rapidly progressive, symmetrical weakness of limbs associated with areflexia/hyporeflexia.
2. Axonal Neuropathy: These have been associated with antibodies to gangliosides GM1, GD1a, GM1, GalNac-GD1a and GD1b present in peripheral nerve axons.

   (a) Acute motor axonal neuropathy (AMAN)-Pure motor and rare cranial nerve involvement. Most cases are preceded by *C. jejuni* infection. No sensory complaints and Deep tendon reflexes (DTR) may be normal.
   (b) Acute motor and sensory axonal neuropathy (AMSAN)-More severe form of AMAN with both motor and predominant sensory deficits.

3. Miller Fischer syndrome (MFS): Typically presents with a triad of bilateral ophthalmoplegia, ataxia and areflexia. Serum Immunoglobulin G antibodies against gangliosides GQ1b, GD3 and GT1a are often present.
4. Bickerstaff brainstem Encephalitis: Encephalopathy and hyperreflexia with features of MFS such as ophthalmoplegia and ataxia and is also associated with anti GQ1b IgG antibodies.
5. Pharyngeal-Cervical-Brachial weakness (PCB): Localized form of axonal GBS affecting the oropharynx causing swallowing dysfunction, neck and upper extremity muscle weakness, as well as facial weakness. Associated IgG antibodies to GT1a or GQ1b antibodies.
6. Bifacial weakness with paresthesias. Facial weakness and limb areflexia/hyporeflexia.
7. Paraparetic GBS: Mild form of GBS with lower extremity weakness and occasional arm weakness but normal bladder function. Diagnosis is supported by presence of sensory deficits, reduced reflexes, or abnormal nerve conduction of the upper extremities.
8. Sixth Nerve palsy and distal paresthesia: is another uncommon variant [14].
9. Acute Pandysautonomia: Symptoms include abdominal pain, vomiting, diarrhea, dizziness, urinary retention, orthostatic hypotension, invariant heart rate, sweating, salivation and lacrimation [14].
10. Pure sensory GBS: Features of sensory ataxia. Antibodies to GD1b.

Guillain-Barré syndrome is usually a clinical diagnosis and there are other differentials to be considered (Table 26.1).

26.4 Investigations

1. Metabolic panel, white blood cell count, creatinine kinase and transaminases.
2. Serology for human immunodeficiency virus, Hepatitis A and B, *M. pneumonia*, Epstein-Barr virus, cytomegalovirus, Zika virus and Lyme disease.
3. Testing for anti-ganglioside antibodies: GQ1b is the only one which is tested because of limited clinical utility of other antibodies.
4. Vasculitis screen to rule out other causes.
5. Chest radiograph.
6. Electrocardiogram-autonomic dysfunction is a very common presentation.
7. Pulmonary function tests. A negative inspiratory force test which can be done at bedside is valuable to detect those with high risk of respiratory compromise [16]
8. Stool culture and serology for *C. jejuni*
9. Urine porphobilinogen and serum delta-aminolaevulinic acid for porphyria.
10. Drugs and toxins screen.
11. Acetylcholine receptor and muscle-specific tyrosine kinase antibodies.
12. Electrodiagnostic studies: To support clinical diagnosis [17, 18].

Table 26.1 Differential diagnosis of Guillain-Barré Syndrome [14, 15]

Central nervous system
• Encephalitis
• Brainstem stroke
• Poliomyelitis affecting the anterior horn cells
• Acute spinal cord lesion
Peripheral nerve system
• Chronic inflammatory demyelinating polyneuropathy
• Critical illness polyneuropathy
• Lyme's disease
• Toxic neuropathy: toxins, heavy metals
• Vasculitis
• Diabetes neuropathy
• Porphyria
Muscle
• Acute inflammatory myopathies
• Periodic paralysis
• Rhabdomyolysis
Neuromuscular Junction
• Myasthenia gravis
• Botulism
• Neuromuscular blocking agents
Others
• Electrolyte disturbances
• Viral infections
• Diphtheria
• Lymphoma
• Paraneoplastic diseases
• Sarcoidosis
• HIV

(a) As the disease process is dynamic serial nerve conduction studies (NCS)/Electromyography (EMG)

- Demyelination features: These findings may be absent during the initial course of the disease. Early finding in AIDP is prolonged F-wave latencies and prolonged tibial nerve H-reflex response or poor F-wave repeatability caused by demyelination of nerve roots. Followed by prolonged distal motor latencies and temporal dispersion or conduction block. Slowing of nerve conduction velocity occurs 2–3 weeks after the onset [17]. Presence of A waves and abnormal blink response. Sural sparing pattern observed in some patients with AIDP has high specificity
- Axonal features: Decreases motor or sensory amplitudes. Sensory nerve studies to differentiate between AMAN and AMSAN. Needle electrodes are probably more useful in AMAN as they reveal reduced recruitment. Reversible conduction failure is observed in AMAN

13. Nerve ultrasound which might be potentially useful by detecting nerve enlargement [19].
14. Cerebrospinal fluid (CSF) analysis: May be normal in the first week of illness in more than 50% of patients [13]. Albuminocytological dissociation in the CSF with an elevated protein level and normal cell counts ≤50/μL.
15. Gadolinium-enhanced MRI brain and spine-which might reveal enhancement of intrathecal nerve roots and cauda equina [17].

26.5 Treatment

Treatment of GBS aims at prevention of severe axonal injury at initial presentation to achieve an effective neurological outcome and prevent disability. Management includes a combination of multidisciplinary supportive medical care and intravenous immunoglobulin or plasma exchange. Hospitalization is required for close hemodynamic monitoring. Several predictive models have been developed to predict the outcomes and need for mechanical ventilation. However pulmonary function tests including forced maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP) and vital capacity may aid evaluation of the respiratory muscle weakness and the individual need for Intensive care unit admission.

26.6 Respiratory Considerations

Prompt recognition of signs and symptoms of impending neuromuscular respiratory failure is paramount in making decisions regarding timely interventions including intubation and mechanical ventilation.

1. Restlessness, confusion, fatigue, sweating
2. Tachycardia-heart rate >100 beats/min
3. Tachypnea-respiratory rate >20 breaths/min
4. Use of accessory muscles of respiration
5. Vital capacity decrease to 20 mL/k
6. MIP decrease to −30 cm H20
7. MEP decrease to 40 cm H20

Tracheostomy should be considered as an option when weaning from ventilation is prolonged.

26.7 Supportive Care

1. Subcutaneous anticoagulation and graduated compression stockings to decrease the risk of deep vein thrombosis in hospitalized patients.

2. Cardiac and hemodynamic monitoring: Autonomic dysfunction causing arrhythmia especially bradycardia and labile blood pressures.
3. Enteral nutrition and monitor bowel and bladder dysfunction.
4. Respiratory monitoring and aspiration precautions.
5. Pain Management.
6. Skin care: Prevention of skin breakdown.
7. Multidisciplinary rehabilitation, skilled nursing care, physiotherapy and psychological support.

26.8 Disease-Modifying Treatment

Plasma exchange (PE) or Intravenous immune globulin (IVIG) are standard treatments recommended for GBS. The American Academy of Neurology does not recommend sequential treatment with PE followed by IVIG [20]. Time period to onset of recovery is shortened by 40–50% by treatment with PE/IVIG. Patients who are already recovering after a mild illness do not require disease-modifying treatment [20, 21].

1. **PE**: The procedure involves replacement of patient's plasma with artificial plasma substitute like donor plasma or 5% albumin solution (preferred) and is usually effective when started within 4 weeks of symptom onset [19, 22]. Wijdicks et al. describe PE to be most effective when started within 7 days of symptom onset [23]. A Cochrane systematic review on plasma exchange assessed the effects in GBS. The authors concluded that moderate-quality evidence shows that plasma exchange is superior to supportive care alone without a significant increase in serious adverse events and after 1 year severe residual weakness is less likely [24].
   (a) **Mechanism of action**: PE removes circulating soluble factors such as immune complexes, complement and biological response modifiers which are responsible for nerve damage and might improve T-cell suppressor function [23].
   (b) **Regimen**: PE usually involves exchange of approximately one plasma volume, 50 mL/kg and varies from four to six treatments, depending on severity of disease and is administered over 1–2 weeks. PE has been shown to improve the time to recover the ability to walk, the need for artificial ventilation, duration of ventilation and measured muscle strength after 1 year [22].
   (c) **Complications of PE**: Allergic reactions, hemodynamic instability, dilutional coagulopathy, sepsis, complication associated with central venous access, electrolyte disturbances.
   (d) **Relative Contraindications**: Pregnancy, active infection, hemodynamic instability, hemostatic disorders.
   (e) PE requires special equipment, is difficult to perform in younger children and huge volume shifts are involved in the process.

2. **IVIG**: IVIG is extracted from pooled purified immunoglobulin from several blood donors. It is as effective as plasma exchange for the treatment of GBS and outcomes are better when administered within 2 weeks of onset of weakness. Choice of treatment depends on availability of resources, patient preferences risk factors and contraindications.
   (a) **Mechanism of action**: Possible modulation of pathogenic autoantibodies, inhibition of complement activation and interception of membranolytic attack complex formation, modulation of expression and function of Fc receptors on macrophages, suppression of T-cell functions and interference with antigen recognition.
   (b) **Dosing**: IVIG is given for 5 days at 0.4 g/kg body weight/day at around 1–3 mL/min [23].
   (c) **Side-effects of IVIG**: Rash, myocardial infarction, aseptic meningitis, acute renal failure and hyperviscosity leading to stroke. IgA deficiency can lead to anaphylaxis.
   (d) **Relative contraindications**: Hypergammaglobulinemia, high triglycerides and increased serum viscosity.

Corticosteroids do not hasten recovery or affect the long-term outcome and clinical trials have demonstrated their lack of efficacy in management of GBS.

Several ongoing trials are ongoing to develop new targeted drug therapy. Safety and efficacy of monoclonal antibody, eculizumab, a complement factor 5 inhibitor thought to prevent complement-dependent neuronal damage is being investigated. Also, an enzyme secreted by *Streptococcus pyogenes* which degrades IgG, possibly destroys pathogenic antibodies and another anti-complement factor 1 antibody seems promising. Many other biological agents are being proposed but they have been experimental in animal models and need further research for implementation in clinical practice.

Outcomes: GB syndrome is a potentially life-threatening disorder. Eighty-five percent of the patients are able to walk independently at 12 months after diagnosis. Relapses occurred in 5–10% of patients after treatment. Twenty-five percent of patients diagnosed with GBS require ventilatory assistance and prolonged hospital course. Mortality rate of 3% increases to 10–20% with associated comorbidities.

26.9 Pain Assessment Tools

Neurologic symptoms in GBS generally consist of motor weakness and areflexia. There has been recent interest in sensory impairment and pain, which tend to have a impact on patients suffering with GBS's long term health and well-being. Some studies have determined that pain is an initial symptom of GBS, however it is not fully recognized as many practitioners do not have full knowledge of disease presentation, as well as the fact that many of these patients may have been on ventilatory support in intensive care units (ICU) and are unable to communicate the severity of pain.

The majority of pain in GBS is generally acute and tends to be seen in a younger patient population and can be seen as an initial symptom in the pediatric population. This acute pain however, can progress to a chronic, debilitating pain, leading to a reduction in the quality of life of a patient. Furthermore, the reported frequency of pain in patients suffering with GBS is variable (55–89%) and is described as moderate to severe and can last up to 1 year in some patients. In one reported study, around 34.5% of the patients reported pain during the acute phase of GBS and another 33.3% of patients reported pain during the 2 weeks preceding the onset of weakness [25]. A variety of tools, such as pain scales as well as diagnostic criteria have been implemented to determine the correlation and severity of pain that these patients experience, as well as their long-term prognosis. In this portion, we discuss these specific indicators [26].

26.9.1 Physical Examination

A key indicator of pain experienced by GBS patients is determined by a detailed physical examination. A large number of patients have complained of lumbar radicular pain especially in the lower extremities, burning pain in the extremities, dysesthesia, paresthesia as well as deep muscle pain in both acute and chronic states of the disease. These symptoms generally occur prior to motor weakness, simultaneously with as well as after motor weakness has occurred. Lumbar pain in GBS is poorly understood and is likely to be multifactorial, possibly due to denervation and inflammation of sensory nerves and tends to be seen in younger patients. Another possible explanation of radicular pain that these patients suffer is entrapment neuropathy, however, this has not been fully investigated.

26.9.2 Numerical Rating Scale (NRS)

This is a numerical scale from zero to ten, in which pain is based on assigning the severity of pain related to a numerical point, where zero is reported as no pain, and ten reported as the worst pain a patient has experienced. Most studies that have been reported on the relationship of pain and GBS use the NRS to determine the severity of pain that their experience.

26.9.3 Visual Analogue Score (VAS)

This is similar to the NRS, as it is a quantitative pain scale using a 10 cm long straight line with the left end of the line labelled “no pain” and the right end labelled “worst pain imaginable”. The distance from left to right is measured and

a numerical value from 1 to 10 is assigned. A major disadvantage of this, is that it allows only a quantitative, unidimensional value is placed on the complex multidimensional pain experience and as such the patient is not able to qualify the severity of pain.

26.9.4 McGill Pain Questionnaire (MPQ)

This is a detailed three portion questionnaire used to determine the severity of a patient's pain.

The first part consists of an anatomic drawing of the human form on which the patient marks where his or her pain is located. The second part of the MPQ allows the patient to record the intensity level of his or her current pain experience. The third part of the MPQ is a pain verbal descriptor inventory consisting of 72 descriptive adjectives. The patient is asked to review this list of pain descriptors and circle the ones that serve to best describe his or her current pain experience. Each section is scored separately, and a total cumulative score is tallied.

A major benefit of this scoring system is that it allows a qualitative as well as quantitative measure of the patient's pain.

26.9.5 Wong Baker Pain Scale

This has been used to quantify patient's pain from a scale of 0 to 10 using a series of six faces which depicts no pain (a pain score of zero, the first face), up to the sixth face, which depicts a face with severe pain, showing a pain score of ten. It allows patients to quantify their pain, even if they are nonverbal or unable to communicate in English. This is particularly useful for determination of pain severity of patients on ventilatory support in ICUs who are not on sedation with limited ability to communicate.

26.9.6 Nerve Conduction Velocities

Previous studies have demonstrated that GBS syndrome associated neuropathic pain affects both large myelinated nerve fibers as well as small unmyelinated fibers. Nerve conduction velocities have been employed for large fibers associated neuropathy, with decreased conduction velocity correlated with an increased risk of large fiber neuropathic pain.

26.9.7 Temperature Sensation

Neuropathic pain related to unmyelinated small fiber disease in GBS has been determined, with differences in cold and heat pain sensations. GBS patients with neuropathic pain had more severe impairment of cold detection thresholds, heat pain thresholds and responses to suprathreshold heat stimuli in the foot compared with those without pain or with non-neuropathic pain.

Small fiber sensory impairment at the acute stage was correlated with the intensity of burning pain and predicted residual neuropathic pain.

26.9.8 Cerebrospinal Fluid Protein (CSFP)

In one particular retrospective study by Yao et al., the incidence of pain is positively correlated with the concentration of CSFP. It is hypothesized that elevated CSFP concentrations would likely stimulate nerve root inflammation and influence inflammation of the afferent sensory nerves leading to abnormal nerve conduction and pain.

In addition, it was also hypothesized that nerve inflammation could also cause elevated CSFP levels in GBS patients. There exists a need for further investigation into the elevated CSFP and incidence of pain in GBS as this was the only study showing this correlation.

26.10 Management of Pain in the Inpatient Setting

Pain is a frequent sequela of GBS, as much as 89% of patients will suffer from pain during their illness. Pain secondary to GBS is often poorly recognized and poorly treated [27]. The severity of pain ranges from no pain to severe, intractable pain. Pain is usually most severe in acute phase and significantly decreases between 2 weeks and 2 months after initial demyelinating symptoms began [28]. The first 2–4 weeks after the onset of weakness is considered the acute phase of GBS where maximal weakness should be reached. Most patient reaching their maximum weakness within 2 weeks. There is controversy to the correlation between disease severity and pain severity. Studies have shown mixed results of the correlation between disease and disability severity and pain severity, from no correlation to both positive and negative correlations. Currently, the mechanism of pain in GBS is not definitively understood, but literature has suggested inflammatory and autoimmune diseases of the nervous system—including but not limited to GBS—cause an increase in reactive oxygen and nitrogen species that leads to oxidative or nitrosative stress which could be the pathogenesis of pain.

GBS pain has been described as both nociceptive and neuropathic in nature, depending on the pain and patient. There is a wide variety in the types of pain associated with GBS, the most common types being radicular pain (29.9%) and muscle pain (29.9%). These are described by patients as a deep pain of the back and lower extremities, or a burning sensation of the extremities. These pains are thought to be caused by nerve root entrapment and/or a functional alteration or spontaneous discharge of the demyelinated nerves, respectively. The duality of the pain can make it tricky to treat with classic opioid or NSAID analgesics which mostly help with nociceptive pain. Pain management has thus turned to alternative treatments such as anticonvulsants, antidepressants, and epidural opioids to provide adequate pain relief for patients with GBS, especially those suffering from its neuropathic pain.

NSAIDs and opioids are found to relieve mostly nociceptive pain in the muscles and joints, and epidural morphine has been shown to provide significant relief of severe episodes of pain in GBS, even burning pains [28]. However, there are significant side effects physicians should monitor for with NSAIDs and opioids. NSAIDs run the risk of gastrointestinal ulcers, internal bleeding, platelet dysfunction, and acute renal or hepatic injury, especially with heavy or prolonged use. NSAIDs are also contraindicated in many patients with bleeding risks, such as those on anticoagulant or antiplatelet therapy, history of gastrointestinal ulcers, those who already frequently use NSAIDs, or those with genetic disorders predisposing them to bleeding, just to name a few. Common opioid side effects include the development of tolerance and/or dependence to opioids, patient sedation, significant constipation, respiratory depression, and many others. While there have been case reports showing effectiveness of prednisone for pain relief in pediatric patients, research has not shown that corticosteroids are effective in the treatment of pain in GBS on a wider scale.

Anticonvulsants, specifically carbamazepine (300 mg/daily) and gabapentin (15 mg/kg daily or 100–300 mg TID), have shown promise in the treatment of both neuropathic and nociceptive pain of GBS. Both are effective analgesics in the pain syndrome of GBS. While both effective, gabapentin has been shown to be superior to carbamazepine for pain relief and reduction of fentanyl rescue analgesia. Epidural infusions of morphine (1–4 mg morphine bolus injections every 8–24 h) have shown "excellent relief of intractable pain" in those with GBS.

While the exact mechanism causing pain in GBS is poorly understood, understanding the mechanisms of action of the medications that cause pain relief can give us insight to its mechanism. NSAIDs work by inhibition of COX-1 and/or COX-2, depending on the NSAID, preventing the production of prostaglandin, a pain and inflammation mediator. Opioids bind specific receptors in the nervous system, directly acting to block pain propagation. Steroids decrease inflammation and were thought to decrease inflammation of the nerves affected by GBS thus providing pain relief, however they have been proven ineffective in GBS pain analgesia overall. Anticonvulsants' mechanism of action in the reduction of pain is still not very well understood but it is known that they enhance GABA's—an inhibitory neurotransmitter—action. This is thought to stabilize nerve cells and block new pain conducting synapses from forming.

Overall, the current literature shows to start with NSAIDs, as they are shown to help with mild muscular aches and pains that commonly occur is GBS. However, NSAIDs frequently do not provide adequate pain relief in patients with this disease and are contraindicated in patients with bleeding risks. After failing a trial NSAIDs it is recommended to begin gabapentin or carbamazepine in an attempt to provide greater pain relief, especially if the pain is neuropathic in nature (i.e.; burning sensations). Even with anticonvulsant therapy, many still have inadequate pain control; therefore, adjuvant therapy with opioids may be necessary. Epidural infusions of morphine have been successful for intractable pain, in one study. Closely monitor patients on opioids for adverse side effects, especially if using fentanyl.

26.11 Discharge Plan for Pain Management

Pain associated with the acute phase of GBS has been recognized since the 1980s; however, pain after hospital discharge may be an underappreciated component of care. A long-term follow-up study found that 38% of patients with GBS reported pain after 1 year. The pain experienced by these patients was rated moderate to severe by the majority of those in the study. Patients experiencing pain in the acute phase of GBS were more likely to have pain upon the later stages. Interestingly, pain intensity was found to be correlated with the severity of weakness, fatigue, and disability in the later stages of disease, but not the acute phase. It is thought that this is related to sensory nerve involvement as opposed to classic pure motor involvement in GBS, but the pathophysiology of this pain is poorly understood. Other intriguing findings of this study were that 36% of patients had pain in the 2 weeks prior to their illness, and 22% of patients in the study had a previous history of chronic pain with half of them taking daily analgesics. Pain was characterized as painful paresthesia/dysethesia, myalgia and joint pain in the chronic phase. The majority of patients with pain at 1 year had symptoms in the extremities (82%); additionally, back pain was seen (36%), interscapular pain (33%), and neck pain (29%). Fifty percent of patients at 6 months had pain in more than one area. There was no association between pain intensity and age, treatment with methylprednisolone, antiganglioside presence, or axonal vs demyelinating GBS. Even with analgesic therapy, approximately 50% patients with pain continued to have moderate pain, and 1 in 3 had severe pain.

The challenges of pain control in patients in the chronic phase of GBS include determining the type of pain, as well whether it is due to their pre-existing pain or the lingering effects of GBS. It is also unclear if the disability seen in the later stages of GBS is due to pain or the pain leads to disability.

Pain in GBS is poorly understood but may be explained by nerve root involvement with radiating nociceptive pain involving the back and extremities. Neuropathic pain may be caused by injury to large myelinated sensory afferents. This type of injury could be the cause of the painful dysethesias often seen in the extremities of

chronic GBS patients. Small nerve fibers related to pain and autonomic dysfunction may be involved as well. Intraepidermal nerve fiber density has been associated with GBS pain in the acute phase of the disease.

Care should initially focus on the likely etiology of the patient's pain, and initiation of the appropriate therapy. Non-opioid analgesic therapy should be emphasized, as patients may develop chronic symptoms for years following their first symptoms. Long-term follow-up with evaluation and treatment of pain should be a part of any discharge plan. As described above, although the analgesic effect of steroids in back pain has been widely studied, several studies have found no difference in pain in GBS patients treated with corticosteroid when compared to those not. Anticonvulsants have become a mainstay of neuropathic pain therapy in the general chronic pain population and may be of benefit for patients in the acute and chronic phases of GBS. A Cochrane review in 2015 found that while the quality of evidence was low, significant reductions in pain with gabapentin and carbamazepine therapy, when compared to placebo, have been demonstrated. Despite these interventions, opioid therapy may be indicated in some patients [29]. It is notable that this recommendation was made in 2005, prior to the current opioid crisis. Studies of IV immunoglobulin have been performed, but the efficacy of its use in GBS remains unclear.

A comprehensive approach to the treatment of pain is crucial, and a multidisciplinary team may benefit the patient's quality of life. Severe fatigue has been found to be present in the majority of patients with previous GBS. Fatigue was also associated with a decrease in measures of quality of life. Physical training in the form of bicycle exercises have been found to lead to relief of fatigue, as well as anxiety and depression in patients with GBS.

26.12 Summary

- GBS is a complex disease associated with pain, therefore, achieving adequate symptom control is difficult and is in need of greater inquiry.
- While the exact pathophysiology of GBS has never been fully described, the medical community has come to accept that GBS is a post-infectious, auto immune-mediated process.
- Early diagnosis of GBS can be complex in clinical practice due to its variable presentation and different clinical subtypes.
- Treatment of GBS aims at prevention of severe axonal injury at initial presentation to achieve an effective neurological outcome and prevent disability.
- Furthermore, GBS pain has been described as both nociceptive and neuropathic in nature, depending on the pain and patient and the mechanism of pain in GBS is not definitively understood.
- Therefore, there remains a continued need for large, high quality studies to better evaluate the putative therapeutics for pain management.

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Chapter 27
The Hypermobile Patient

Nathan J. Rudin

27.1 Introduction

Hypermobility disorders are inherited conditions causing laxity of connective tissue. The Ehlers-Danlos syndromes (EDS) and generalized hypermobility spectrum disorder (G-HSD) are the most common hypermobility conditions. Hypermobility is also seen in Marfan syndrome, Loeys-Dietz syndrome, Down syndrome, Noonan syndrome and numerous other congenital disorders.

Joint laxity is the most obvious sign in the majority of hypermobility conditions, and may cause increased susceptibility to joint injury and spinal instability. Laxity may also be present in other tissues including the oropharynx, skin, cardiovascular structures, viscera, and tissue supporting nerves. Hypermobile individuals are also prone to low baseline blood pressure, orthostatic intolerance, and other difficulties. Special care and caution are required to address pathology related to hypermobility while minimizing the risk of complications during hospitalization and surgery.

27.2 Pathophysiology

Hypermobility conditions result from molecular defects in collagen and/or other proteins supporting collagen function. Many of these disorders have known genetic causes, though the molecular basis of hypermobile EDS and G-HSD (the most common hypermobility conditions) remains unknown [1].

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27.3 Diagnosis

- **General History.**
  - History of hypermobility or being "double-jointed." Many hypermobile individuals are aware of being more flexible than normal.
  - Hypermobile individuals may perform contortions or unusual movements with their joints, mostly during childhood. Many have a habit of "cracking" joints for comfort.
  - History of athleticism: gymnastics, swimming, dance, and other activities are common pursuits, especially during childhood through teenage years.
  - Frequent sprains, strains, or other musculoskeletal injuries disproportionate to the causative activity. Frank joint dislocations may occur, especially at shoulders and patellae.
  - Scoliosis may be present.
  - Foot/ankle alignment problems may present in childhood and require early orthotic intervention.
- **Family History.**
  - Hypermobile joints.
  - Early and/or extensive osteoarthritis.
  - Scoliosis.
  - Aneurysms, arterial dissections (vascular type Ehlers-Danlos syndrome, Loeys-Dietz syndrome, Marfan syndrome).
- **Symptoms.**
  - Focal or diffuse joint pain.
  - Diffuse muscular pain.
  - Easy bruising.
  - Fragile skin.
  - TMJ pain, crepitation, limited mouth opening, jaw dislocation [2].
  - Postural lightheadedness (not vertigo), precipitated by rapid standing, treated with sitting, lower limb elevation, supine position. Patients with orthostatic intolerance may habitually drink large amounts of water and may crave salty foods [3]. Etiology of these symptoms is unclear.
  - Palpitations and orthostatic tachycardia.
  - Paresthesias associated with nerve irritation, compression or entrapment. Lax connective tissue surrounding nerves may cause subluxations and increased vulnerability to compression.
  - Abdominal pain. Diarrhea and/or constipation. Heartburn and/or reflux. Food intolerances [4].
  - Chronic headache (migraine or other types).
  - Cold hands/feet; Raynaud phenomenon is common.
  - Tooth pain, jaw pain with crepitation or dislocation, advanced caries, tooth fragility. Oral pain complaints are common [5]. Severe periodontal disease is a hallmark of the rare periodontal-type EDS (pEDS) [6].

- Neck and/or back pain, with or without radiculopathy.
- Heightened allergic/hypersensitivity reactions; provoked or spontaneous flushing, swelling, urticaria. Some patients have documented mast cell hyperfunction disorders [7].

- **Signs.**
  - Joint hypermobility.

    The most common assessment tool is the Beighton score (Fig. 27.1) [8], which is recommended whenever a hypermobility disorder is suspected.

    Other hypermobile joint findings may include:
    - Extension of first metatarsophalangeal joint past 90°.
    - Hypermobile patellae with respect to femurs.
    - Glenohumeral instability: increased AP translation of humerus with respect to femur, increased internal rotation, "sulcus sign" with gentle inferior traction on the humerus.
    - Increased hip mobility: abduction, internal rotation, external rotation.

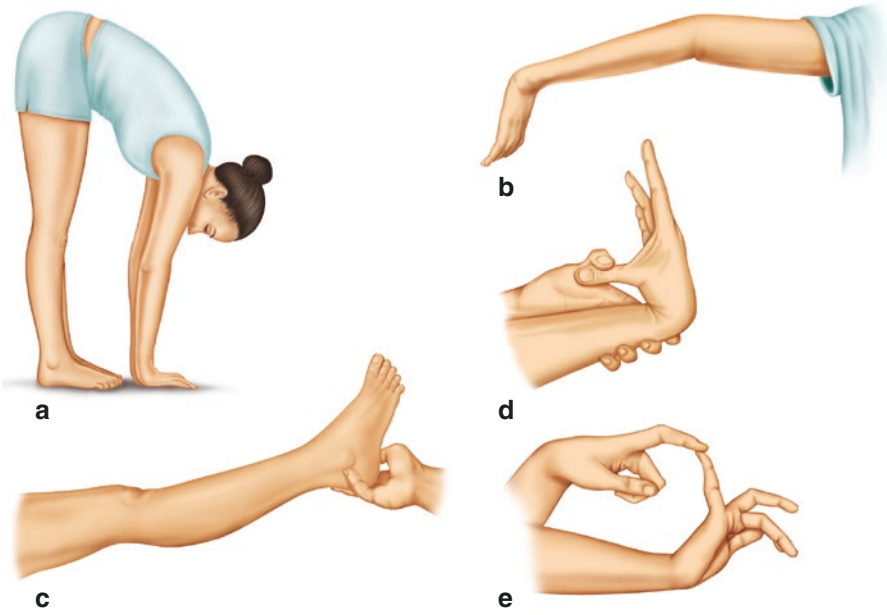

Fig. 27.1 Beighton Hypermobility Scale. This scale is scored by assessing for the following: (**a**) Ability to flex forward at the waist while standing and bring palms flat to the floor without bending the knees: 1 point. (**b**) Hyperextend the elbow beyond 10°: 1 point for each elbow. (**c**) Hyperextend the knee beyond 10°: 1 point for each knee. (**d**) Passive apposition of the thumb to the flexor aspect of the forearm: 1 point for each hand. (**e**) Passive extension of the fifth metacarpophalangeal joint beyond 90°: 1 point for each hand. Possible score range: 0–9 points. (Adapted from: Beighton et al. [8])

- Postural abnormalities.
  Rounded shoulders, increased lumbar lordosis, knee hyperextension during stance, increased thoracic kyphosis (especially when seated), flat feet, ankle valgus. Some individuals demonstrate an abnormally flattened thoracic kyphosis, with accompanying restrictions in rib mobility causing chest discomfort and restricted inspiratory capacity.
- Skin abnormalities.
  Soft, hyperextensible and/or translucent skin.
  Wide, atrophic scars may be present (classical Ehlers-Danlos syndrome, others).
  Extensive bruising.
- Osteoarthritis, often diffuse, may be of early onset.
- Scoliosis or kyphoscoliosis.
- In pregnant women: premature rupture of membranes, cervical incompetence; vascular EDS may cause placental abruption, peripartum uterine and/or arterial rupture [9].

- **Investigations.**
  - X-rays may indicate presence of osteoarthritis.
  - Spinal X-rays, MRI, CT to assess for degenerative disc/facet disease, spinal segment instability, disc herniation, Chiari I malformation; all are associated with hypermobility [10].
  - Transthoracic echocardiogram will assess for valvular prolapse, aortic dilatation [11]. Low threshold for this test in patients with profound hypermobility, heart murmur or click, other evidence of vascular insufficiency.
  - Angiography, especially head/neck and chest/abdomen, is indicated if vascular EDS is suspected; screen for aneurysms, dissections.
  - Orthostatic vital signs and/or tilt-table testing may be useful to screen for autonomic dysfunction in individuals with orthostatic intolerance [3].
  - Upper endoscopy, barium studies, gastric emptying studies can identify hiatal hernia, esophageal sphincter laxity, gastroparesis [4].
  - In pregnant women: Pelvic exam, assess cervical competence, fetal ultrasound.
  - Molecular genetic testing to confirm suspected disorder(s), if diagnosis is felt to be critical to management.

- **Pain Assessment Tools:** Standard tools can be used.

Prevention. Preventive measures may reduce the likelihood of new pain conditions developing during hospitalization.

- Positioning and skin/nerve integrity: In the hospital bed and in the operating room, care must be taken to reduce the risk of pressure injuries to fragile skin or commonly entrapped nerves [12]. In the OR, protect vulnerable nerves (peroneal at fibular head, ulnar at cubital tunnel) through padding and careful positioning. For patients in bed, frequent position changes to shift weightbearing, and padding or splinting of vulnerable areas, can reduce injury risk.

- Surgical closure: Patients with abnormally lax tissues may require extra attention to cutaneous and deeper tissue closure due to increased risk of dehiscence and hernia.
- Airway management: Extra care may be required during endotracheal and other intubation to reduce risk of injuring the jaw joints, teeth, or cervical spine. TMJ subluxation can occur during mask ventilation [13].
- GI management: Risk of GE reflux is increased in some patients with lax esophageal sphincters and/or hiatal hernias. Vocal cord prolapse or reduced pharyngeal muscle tone may complicate reflux management and airway protection [14]. Elevating the head of the bed may reduce reflux and aspiration risk, as may initiation or optimization of antireflux medications.
- Vascular procedures: Vascular EDS, Loeys-Dietz syndrome and some other conditions pose increased risk of arterial injury or rupture. Increased compression time may be needed after procedures requiring arterial puncture.
- Cardiovascular management: Given a high incidence of orthostatic intolerance and/or orthostatic hypotension, hypermobile individuals require close intraoperative hemodynamic monitoring and may require modified anesthetic regimens. The use of graduated compression stockings will reduce orthostatic symptoms.
- Joint replacements: Some hypermobile patients benefit from modified surgical techniques to minimize soft-tissue disruption, and constrained prostheses [15] to decrease the risk of instability.
- Pharmacotherapy for pain: Local anesthetics may not work fully or at all in some hypermobile individuals, for reasons as yet unknown [16]. Consider a test dose of subcutaneous lidocaine if planning to employ local anesthetics as a major anesthetic modality. Anecdotally, some individuals who do not respond to lidocaine have better effect from bupivacaine or other local anesthetics.

Treatment. Most pain treatment for hypermobile patients is the same as for those without hypermobility; preventive measures (see above) have paramount importance during the inpatient stay. Specific treatment issues include the following.

- Physical and Occupational Therapy: Considered mainstays of hypermobility management, though evidence base remains scant [17]. Extra attention must be paid to joint stability, with increased care as the patient resumes ambulation. Postural abnormalities should be identified and addressed with exercise and activity modification.
- Orthoses: Splints and braces may help stabilize hypermobile ankles, knees, shoulders, and other joints to reduce pain and injury as rehabilitation proceeds.

27.4 Challenges in Management of Pain While in the Hospital

- Pharmacotherapy: Resistance to local anesthetic effects may reduce the utility of lidocaine for systemic or topical analgesia. Consider alternate medications if an appropriate trial of lidocaine is unsuccessful.

- Allergy/hypersensitivity: Individuals with mast cell overactivity may benefit from the concurrent use of H1 and H2 blockers, cromolyn, and corticosteroids if needed, to address flushing, edema, urticaria, and/or asthmatic symptoms [18].

27.5 Discharge Plan for Pain Management

- Follow up with primary care team.
- Where available, refer to a physiatrist (rehabilitation physician) with expertise in hypermobility conditions.
- Arrange outpatient rehabilitation with therapists skilled in managing the hypermobile patient.
- Adjust and/or taper medications as appropriate to the nature of the patient's pain condition.

27.6 Summary

- Confirm hypermobility diagnosis.
- Institute preventive measures: positioning, airway management, surgical tissue closure, reflux management, and others where pertinent.
- Start rehabilitation as soon as possible, with special attention to joint stability.
- Use orthotics as needed to support painful and/or unstable joints.
- Anticipate and treat orthostatic hypotension and/or tachycardia.

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Chapter 28
Patient with Fibromyalgia

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28.1 Introduction

Fibromyalgia is a complex condition of widespread pain that historically has been difficult to diagnose and manage. Once thought to be a disease process of psychosocial underpinnings, fibromyalgia is now thought to be an altered state of pain processing known as central sensitization based on functional imaging studies and biomarker assays. This ultimately leads to increased sensitivity to external stimuli and a diagnosis based on the number of stimuli required to elicit pain and its specific location. Further research led to new diagnostic criteria that encompass the breadth of the disease process, including clinical features such as fatigue, un-refreshed sleep, and cognitive symptoms. An additional challenge in the diagnosis and management of fibromyalgia is that the condition often occurs in conjunction with other disease processes or may be exacerbated by an acute process. This becomes relevant in the inpatient setting when a patient's widespread pain can be generated or exacerbated by the acute disease process or by a progression of the chronic disease that leads to hospital admission.

28.2 Pathophysiology

Since the 1900s, widespread pain has been recognized as a disease. Initial notions of etiology were thought to result from an inflammatory process involving connective tissue or to be psychogenic in nature. The term fibromyalgia was coined in the 1970s and by the 1990s the American College of Rheumatology (ACR) had devel-

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oped the first diagnostic criteria for fibromyalgia, describing patients with chronic widespread pain at 11 out of 18 defined tender points [1]. Armed with an established criteria for diagnosis, research into the disease process expanded and it became apparent that clinical features of fibromyalgia also included central nervous system (CNS) facilitated symptoms such as fatigue, memory difficulties, and disorders of mood and sleep. In 2010, ACR developed new diagnostic criteria that replaced the tender points elicited upon physical exam with a widespread pain index and symptom severity scale. The current focus on a pathophysiologic mechanism for the constellation of symptoms experienced by the fibromyalgia patient has been linked to an altered central sensory processing.

Functional neuroimaging studies have been particularly useful in supporting aberrancies in central sensory processing. For example, Gracely et al. showed a statistically significant increase in brain activity in areas associated with pain processing in fibromyalgia patients compared to controls exposed to the same stimulus [2]. Studies of resting-state analysis functional magnetic resonance imaging (fMRI) reveal increased resting state connections of the brain with the insula and decreased resting state connections of the brain with antinociceptive regions [3]. A recent study by Martucci et al. performed resting state fMRI of the cervical spinal cord in fibromyalgia patients and compared them to healthy controls. The findings reveal greater ventral and lesser dorsal spinal cord activity in fibromyalgia patients, which may indicate central sensitization [4]. Also, single-photon emission computed tomography (SPECT) used to study the pathogenesis, showed increased perfusion in the somatosensory cortex and a reduction in other regions of the brain [5]. SPECT scans have demonstrated changes in resting cerebral blood flow (rCBF) that is altered during treatment with medications such as amitriptyline in fibromyalgia patients [6].

In addition to functional neuroimaging, magnetic resonance (MR) spectroscopy is also useful in uncovering aberrancies in central sensory processing in fibromyalgia patients. Elevated levels of neurotransmitters that facilitate the wind-up and central sensitization phenomena in areas of the central nervous system involved in pain processing [7]. Interestingly, these levels change as patients are treated. Studies show elevated levels of substance P in the cerebral spinal fluid (CSF) and reduced serum levels of serotonin and its metabolite 5-hydroxyindoleacetic acid and the metabolite of norepinephrine 3-methoxy-4-hydroxyphenethylene in CSF in fibromyalgia patients [8, 9]. This imbalance of enhanced excitability and reduced inhibition as a pathogenic mechanism is also supported by the efficacy of medications used to treat the disease, such as tricyclic antidepressants (TCAs) and duloxetine that increase levels of serotonin and norepinephrine. Opioids have not been found to be efficacious in the management of fibromyalgia because of suspected high levels of endogenous opioids already bound to receptors in these patients. This theory is supported by positron emission tomography (PET) imaging that reveals reduced opioid receptor binding, and by studies of CSF levels of enkephalins in fibromyalgia patients compared to controls [10, 11].

Genetic studies play a role in uncovering the pathophysiology behind fibromyalgia. The familial patterns have led researchers to focus on polymorphism in genes encoding proteins, such as serotonin transporters and catechol-O-methyltransferase enzyme (COMT), that result in derangements in CNS neurotransmitters [12, 13].

It is well established that the immune system plays a role in many different pain states. Aberrations in the immune system of fibromyalgia patients have been pre-

sented as an additional pathophysiological mechanism of the disease. Immune function studies have shown specific increases in levels of IL-6 and IL-8, which in vitro can be stimulated by the pro-nociception neurotransmitter substance P [14].

The clinical features of fibromyalgia—including diffuse widespread pain, cognitive difficulties, fatigue, and mood disorders—led researchers to focus on augmented central sensory processing as a unifying pathophysiological mechanism. Advances in functional imaging techniques, MR spectroscopy, pharmacology, immunology, and genetics provided evidence to help support this notion. Understanding the etiology of augmented central processing that occurs in fibromyalgia will ultimately lead to successful diagnosis, management, and prevention.

28.3 Diagnosis

The diagnostic criterion of fibromyalgia has evolved since the 1970s when Smythe and Moldofsky first labeled the disorder "fibrositis syndrome." The diagnostic criteria for this first iteration of the disorder included pre-specified tender points, widespread aching lasting longer than 3 months, and disturbed sleep with morning fatigue and stiffness. The diagnosis focused largely on tender points and, until the late 1980s, any changes made to the diagnostic criteria were simply about the number of tender points required for diagnosis. By the early 1990s, the ACR's criteria for research classification of fibromyalgia included the following: chronic widespread (four quadrants) soft tissue pain for 3 months and pain induced by 4 kg of digital palpation pressure at 11 of 18 anatomically defined tender points (Fig. 28.1). The reported sensitivity and specificity was >80% [15]. In 2010, the diagnostic criteria for fibromyalgia was re-evaluated largely because the tender point exam had significant variability among physicians and was often performed incorrectly. Focusing on tender points overlooked other significant clinical features such as non-refreshing sleep, mood disorders, and cognitive disabilities [16].

In 2010, the ACR replaced the tender point exam with a widespread pain index that measured the number of areas a patient experienced pain over the previous week on a scale from 0 to 19. The second component of the diagnostic criteria included a symptom severity (SS) score, which assesses the severity of the associated symptoms of fatigue, un-refreshed sleep, and cognitive issues. Each symptom is scored on a scale from 0 to 3 representing no problem, slight or mild, moderate, and severe over the past week respectively. An additional scoring of 0–3 representing no symptoms, few, moderate, and a great deal is given for the same somatic symptoms in general. Total symptom severity is scored on a scale from 0 to 6 [17]. Patients who meet the following three conditions meet the criteria for a diagnosis of fibromyalgia:

1. Widespread pain index (WPI) > or equal to 7 and symptom severity (SS) score of greater or equal to 5 or a WPI between 3 and 6 and SS score greater than or equal to 9
2. Symptoms present at similar levels for at least 3 months
3. Patient has no disorder that would otherwise explain the pain

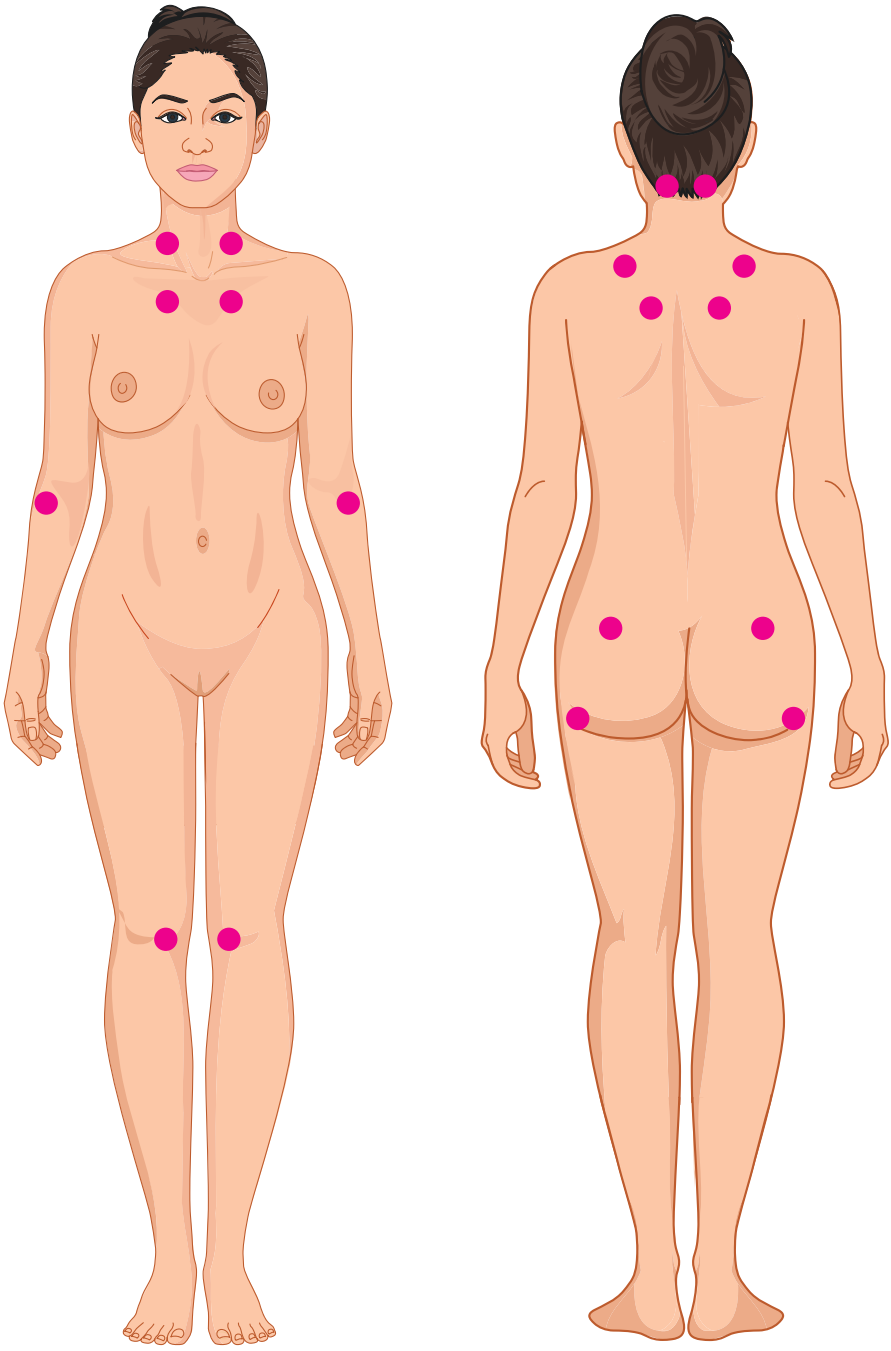

Fig. 28.1 Tender points in fibromyalgia

In 2011, the authors published an update to their criteria, adding a diagnostic self-survey for research purposes rather than clinical. They developed a "fibromyalgia severity score" that is the sum of the widespread pain index and symptom severity scale. The score provides the means to quantify the severity of a patient's disease process.

In 2016, another update was introduced to help minimize misclassification of regional pain disorders and to clear up any confusion surrounding the diagnostic exclusions (Table 28.1). These changes led to four criteria for diagnosis, including:

Table 28.1 Fibromyalgia criteria

ACR 2016 fibromyalgia criteria revision
A patient must meet three of the following conditions: 1. Widespread pain index (WPI) ≥ 7 and a symptom severity (SS) score ≥ 5 or a WPI of 4–6 and SS score ≥ 9 2. Generalized pain in at least 4–5 regions must be present; jaw, chest and abdominal pain are not included in a generalized pain definition 3. Symptoms present for at least 3 months 4. A diagnosis of fibromyalgia is valid irrespective of other diagnoses; a diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses
Widespread Pain Index
Note the number of areas in which the patient has had pain over the past week. In how many areas has the patient had pain? Score is between 0 and 19
Left upper region (Region 1) and right upper region (Region 2)
Jaw, shoulder girdle, upper arm, lower arm
Left lower (Region 3) and right lower (Region 4)
Hip (buttock, trochanter), upper leg, lower leg
Axial region (Region 5)
Neck, upper back, lower back, chest, abdomen
Symptom Severity Score (Part 1)
Symptoms
Fatigue
Waking Un-refreshed
Cognitive symptoms
Indicate the level of severity of these symptoms over the past week with the following scale: 0 = No problem 1 = Slight or mild, generally mild or intermittent 2 = Moderate, considerable problems often present and/or at a moderate level 3 = Severe, pervasive, continuous life-disturbing problems
Symptoms Severity Score (Part 2)
Sum of the severity of the above three symptoms (0–9) plus the sum of the number of the following symptoms (0–3) the patient is bothered by that which occurred during the previous 6 months: • Headache (0–1) • Pain or cramps in the lower abdomen (0–1) • Depression (0–1)
The final symptom severity score is 0–12
The Fibromyalgia severity scale is the sum of the **WPI** and **SS score**
Adapted from 2016 Revisions to the 2010/2011 Fibromyalgia Diagnostic Criteria Wolfe et al. [16]

1. Generalized pain, defined as pain in at least 4–5 regions
2. Symptoms present at a similar level for at least 3 months
3. WPI greater than or equal to 7 and SS score greater than or equal to 5, or WPI of 4–6 and SS score greater than or equal to 9
4. A diagnosis of fibromyalgia is valid irrespective of other diagnoses; a diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses

In a review of validation studies by Wolfe et al., the reported sensitivity and specificity of these criteria are 86% and 90% respectively.

28.4 Treatment

Fibromyalgia treatment aims to reduce pain and concomitant symptoms, including fatigue, stiffness, emotional distress, and cognitive dysfunction (Table 28.2) [18]. Patient engagement is particularly important as many non-pharmacologic modalities are used to elicit long-term success.

28.4.1 Non-pharmacologic Management

The most extensively studied non-pharmacologic therapies include patient education, cognitive behavioral therapy (CBT), and exercise. The role of CBT in the treatment of fibromyalgia has been well supported through meta-analysis, randomized

Table 28.2 Management of fibromyalgia

Approach to Fibromyalgia Treatment
• Educate all patients about the nature of their condition and counsel them on the role of exercise, cognitive behavioral therapy, stress reduction, and sleep
• Perform a comprehensive assessment of pain, function, and comorbid conditions
– Diagnose and treat secondary fibromyalgia associated with other rheumatologic disorders
– Treat concurrent peripheral pain such as arthritis or regional pain disorders
• Consider pharmacologic therapy for patients with severe pain or sleep disturbance; guide medication choice by the predominant symptoms that accompany pain, for example:
– Initial therapy includes a trial of a low-dose tricyclic medication (amitriptyline or cyclobenzaprine)
– If comorbid depression or severe fatigue consider SNRI
– If comorbid anxiety or sleep disorder consider a trial of gabapentoids
– For refractory patients, it is often necessary to use a combination of medications in different classes
– Evidence does not support the use of opioids
– NSAIDs can be used to treat comorbid pain generators but are not proven to improve peripheral fibromyalgia tender points

controlled trials, and observational studies [19]. Originally developed to target mood disorders, CBT has been adapted to treat various chronic pain conditions. The treatment blends cognitive processing distraction, guided imagery, cognitive restructuring and behavioral techniques, activity pacing, relaxation training, and adaptive behaviors. When compared to patient education alone, CBT is associated with reduced pain-related catastrophizing [20]. The suspected neural mechanism of this finding relates to decreased signaling between the primary somatosensory cortex and the insula where bodily sensations and afferents from regions implicated in emotional processing converge [21].

The 2017 European League Against Rheumatism (EULAR) guidelines for managing fibromyalgia support exercise with a "strong" recommendation [22]. The reviewed trials, including a total of 2494 patients, found exercise to have a positive impact on both pain and physical function. The EULAR recommended exercise program consists of ≥20 min aerobic activity 2–3 days per week and ≥8 repetitions per strength exercise 2–3 times per week. Patients unable to complete low-impact exercises or those with continued physical limitations despite an exercise program should be referred to a physiatrist or physical therapist for further evaluation and treatment. Additional exercise programs focusing on mind-body interventions, including yoga and tai chi, may help improve function but have been the subject of few controlled studies.

28.4.2 Pharmacologic Management

Despite the presence of peripheral tender points, peripheral pain medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids have little effectiveness in the management of fibromyalgia pain. Medications aimed at the treatment of central and neuropathic pain are utilized. Three medications are currently approved by the U.S. Food and Drug Administration (FDA) for fibromyalgia treatment: duloxetine, milnacipran, and pregabalin. The American Pain Society and EULAR have evaluated the use of several medications, including pregabalin, gabapentin, duloxetine, amitriptyline, cyclobenzaprine, tramadol, and milnacipran. The classification, dose, effects on fibromyalgia, and adverse effects are described in Table 28.3 [22, 23].

Tricyclic compounds used to treat fibromyalgia symptoms include antidepressants and muscle relaxants such as amitriptyline and cyclobenzaprine. At doses lower than those used to treat depression, amitriptyline has been shown to reduce pain, fatigue, and depressive symptoms [24, 25]. Due to the anticholinergic and sedating effects, it is best taken before bed and caution should be used when prescribing to the elderly and those sensitive to sedation. Although cyclobenzaprine has minimal anti-depressant efficacy, the tricyclic structure is thought to account for the medications effect on fibromyalgia. The degree of benefit was found to be similar for patients taking cyclobenzaprine or amitriptyline; however, side effects were more frequent in those taking cyclobenzaprine [26].

Table 28.3 Pharmacological management for fibromyalgia

Medication	Classification	Dose	Effect on fibromyalgia	Adverse effects
Amitriptyline	Tricyclic antidepressant	Starting dose of 10 mg at bedtime, titrate up to 25–50 mg	Effective on wide range of symptoms, including pain, sleep, bowel, and bladder	Anticholinergic effects, drowsiness
Cyclobenzaprine	Tricyclic, central muscle relaxant	Starting dose of 10 mg at bedtime. Varied final dose from 10 mg in the morning with 20–30 mg at night, up to 10 mg three times a day	Reduced pain and sleep disturbance	Drowsiness, dizziness, xerostomia
Duloxetine	Serotonin and norepinephrine reuptake inhibitor	Start 30 mg daily, gradually increase by 30 mg to target dose of 60–120 mg	Improved depressive symptoms and reduced pain	Nausea, headache, xerostomia, tachycardia, hypertension
Milnacipran	Serotonin and norepinephrine reuptake inhibitor (SNRI)	Start 12.5 mg daily, increase up to 50 mg twice daily	Improved depressive symptoms and reduced pain	Nausea, headache, more likely to cause hypertension
Pregabalin	Membrane $\alpha_2\delta$ calcium channel modulator	Start dose of 25–50 mg at night, increase up to 300–450 mg/day	Improved sleep, fatigue, health-related quality of life	Dizziness and somnolence
Tramadol	Weak opioid, mild SNRI activity	37.5 mg combined with acetaminophen	Reduced pain	Constipation, nausea, dizziness, headache

Patients that do not respond to tricyclic medications, a trial of pregabalin, duloxetine, or milnacipran should be considered. In a meta-analysis of 2249 patients, duloxetine was more likely than placebo to reduce pain by 50% in the short-term (12 weeks) and long-term (28 weeks) [27]. The continued benefit has been studied up to 6 months in patients taking 60 or 120 mg [28]. Milnacipran has more noradrenergic effect than duloxetine and therefore is potentially more helpful for patients suffering from memory problems and severe fatigue. Pregabalin is an anticonvulsant and its efficacy in treatment of fibromyalgia was demonstrated in a meta-analysis of five placebo-controlled studies showing reduced pain, improved sleep, and improved health-related quality of life [29].

Several randomized controlled trials have failed to show the benefit of naproxen, ibuprofen, and corticosteroids. Also, there is no evidence of long-term or short-term benefit for use of pure opioid agonists. Combination therapy should be considered in patients with symptoms refractory to single therapy. Trials of low dose SNRI in

the morning with low dose tricyclic antidepressants in the evening showed superior pain control compared to either medication alone or placebo [30]. Fibromyalgia patients taking combinations of duloxetine and pregabalin reported superior pain reduction, improved sleep and function [31]. Patients prescribed combinations of serotonergic medications should be cautioned to monitor for the signs of potentially life-threatening serotonin syndrome.

28.4.3 Interventions

Few studies have been conducted to document the response of fibromyalgia patients to interventional procedures. Fibromyalgia mediated myofascial pain is hypothesized to be centrally mediated and thus is thought to not respond well to traditional myofascial treatments. One study found that patients with fibromyalgia and peripheral pain generators, trigger point, or joint pain, treating these regional pain disorders was associated with a decrease in fibromyalgia symptoms [32].

28.4.4 Other Modalities

Neuromodulation techniques offer promising options for patients with refractory pain. Transcranial direct current stimulation is used to non-invasively modulate brain activity and has been shown to decrease pain in patients with refractory central pain. Transcranial direct current stimulation over the primary motor cortex is associated with significantly greater pain relief than patients receiving sham stimulation or over the dorsolateral prefrontal cortex in fibromyalgia patients [33].

28.4.5 Pain Assessment Tools

The two main diagnostic tools utilized in accessing symptom severity and associated dysfunctions in fibromyalgia are the fibromyalgia severity scale (FS) and the symptom severity (SS) scale. The FS is determined by the summation of the widespread pain index (WPI). The SS scale provides a quantitative metric for symptom intensity [34]. Scores range from 0 to 31 with a score of 12 required for a diagnosis of fibromyalgia.

The fibromyalgia impact questionnaire (FIQ) was developed to capture the comprehensive spectrum of features associated with fibromyalgia, including physical function, work status, depression, anxiety, morning fatigue, pain stiffness, and well-being over the past week [35]. The self-administered questionnaire includes

10 items that are answered on a scale of 0–10. Each item's score is added up to generate the patient's final score with higher scores indicating a greater impact of fibromyalgia on function. On average, fibromyalgia patients score around 50 with scores above 70 representing severely affected patients [36]. Other useful pain assessment tools include those that evaluate for associated depression such as Beck's Depression Inventory and for catastrophizing behaviors such as the Pain Catastrophizing Scale.

28.4.6 Management of Pain in the Inpatient Setting

Fibromyalgia can be very challenging to treat in an inpatient setting because of the myriad systems that are affected and the heterogeneity associated with the disorder [37]. Pain and musculoskeletal mediated pathology are purported to be the most common reasons for inpatient hospitalization. Other reasons include genitourinary, gastrointestinal, cardiovascular issues, and depression [38]. The presence of acute pain symptomatology superimposed onto fibromyalgia pain can be challenging to treat. An essential step in the treatment of fibromyalgia is identifying and acknowledging the patient's history of chronic pain. Recognizing and treating associated symptoms of fibromyalgia, such as fatigue, anxiety, depression, and headache is essential [39]. Treating the comorbidities with appropriate pharmacological and non-pharmacological interventions improves pain scores and patient satisfaction [40]. Cognitive behavioral therapy has been shown to reduce lifetime pain severity and improve functional status [41].

28.4.7 Challenges in Management of Pain While in the Hospital

A key challenge in fibromyalgia inpatient pain management is identifying the etiology of pain and differentiating chronic pain from an acute pain trigger that led to hospitalization. For example, acute post-surgical pain after a necessary surgery can be challenging to treat in patients with fibromyalgia because their chronic pain states may have led to hyperalgesia, central pain sensitization, and amplification. The lowest possible dose of opioids needed to achieve pain control should be used along with a multimodal regimen.

Healthcare providers who are not familiar with fibromyalgia and its associated symptomatology may feel ill-equipped to provide adequate care. The goal in this situation is to avoid medications and modalities that are of limited benefit in this patient population. Often, patients with fibromyalgia are hyperaware of their symptoms. Their knowledge may be incorrectly perceived as malingering or attempting to achieve some sort of secondary gains rather than a true organic nature.

28.4.8 Modalities and Medications to Avoid

Fibromyalgia is a disorder characterized by centrally mediated pain and sensitization of the CNS. Medications such as NSAIDs and topical analgesics are of limited benefit as they primarily target peripheral pain pathways. Although opioids mediate central pathways, administration of this class of medications should be limited due to the well-known risk of tolerance, hyperalgesia, addiction, and other adverse effects.

28.4.9 Safe Modalities and Medications

A multimodal analgesic approach that targets both the somatic and psychological components of pain is critical in the management of fibromyalgia pain. In the inpatient setting, continuing the patient's pre-admission neuropathic medications is essential. These medications may include but not be limited to antidepressants, SSRIs, SNRIs, and anti-epileptic drugs such as gabapentin and pregabalin. Antidepressants appear to have superior efficacy in the treatment of fibromyalgia pain [39]. Selective hypnotics such as zopiclone or zolpidem may alleviate some sleep disturbances and fatigue but not the associated pain. Tramadol, a weak opiate, can be effective in some cases. Ketamine infusions have been used as effective adjuncts in fibromyalgia [42]. Muscle pain, muscular hyperalgesia, and referred pain are attenuated partly through the antagonistic effect on the N-methyl D-aspartate (NMDA) receptor by ketamine.

Other conservative and non-pharmacological modalities that have been shown to have beneficial effects on treating fibromyalgia pain include TENS units, biofeedback, laser therapy, dry needling, and trigger points. Heat producing modalities such as therapeutic ultrasound or aqua therapy are safe and beneficial in this patient population. Choosing medications with favorable side-effect profiles may also indirectly help associated symptoms (i.e., using amitriptyline for its antidepressant and pain alleviating effects and its sedating side-effect can be beneficial for treating insomnia).

28.4.10 Discharge Plan for Pain Management

Fibromyalgia can be debilitating if not treated appropriately. A multimodal and multidisciplinary approach should be used. Upon discharge from the inpatient setting, it is important to schedule follow-up appointments with the patient's primary doctor, chronic pain specialist, occupational therapist (with an emphasis on body mechanics and energy conservation), physical therapist, outpatient psychologist or psychiatrist, and counselors. These appointments are essential to reduce readmis-

sion rates, reaffirm coping strategies, and improve overall quality of life. Further, long-term treatment for fibromyalgia includes cognitive behavioral treatment programs, which have been shown to decrease pain intensity and interference with daily life and to improve emotional variables [43].

A study by Thieme et al. discussed the utility of operant behavioral treatment (OBT), focusing on changing inappropriate pain behaviors, moderating maladaptive thoughts, and emphasizing coping strategies [44]. When used in conjunction with cognitive behavioral therapy (CBT), physical therapy, and an appropriate medication regimen, OBT can improve outcomes. Studies showcasing the use of Internet-based CBT show promise in treating mild to moderate depression and anxiety in patients with fibromyalgia, and allow for ease of access in populations that would otherwise not be able to participate in CBT [45]. In an outpatient setting, alternative medical modalities such as myofascial release, acupuncture, and massage therapy can be helpful. Patients with fibromyalgia pain have both somatic and psychosomatic components to their pain and addressing pain pathways across various physiological systems will result in optimal outcomes.

28.5 Summary

- Perform a thorough history and physical examination
- Continue patient's pre-admission medications and treatment modalities, such as neuropathic agents, TENS units, and heat producing modalities if possible
- Use pain assessment tools validated for fibromyalgia
- Treat associated symptoms with appropriate therapeutic regimens (i.e., treat IBS symptoms with bulking agents and insomnia with better sleep hygiene or low dose trazodone)
- Use a multimodal approach when treating pain and avoid medications that do not provide significant relief in patients with fibromyalgia, such as NSAIDs and opioids
- Use regional anesthesia when applicable
- Acknowledge the patient's pre-existing chronic pain using tools such as the fibromyalgia assessment questionnaire to increase patient rapport and improve treatment
- Address and treat associated symptoms commonly seen in fibromyalgia such as insomnia, fatigue, headache, and depression

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Chapter 29
Patient with Traumatic Brain Injury

Michael Suer and Alaa Abd-Elsayed

29.1 Introduction

The patient with either acute or chronic traumatic brain injury (TBI) can be a management difficulty for many physicians unless they see such pathology on a regular basis. Even so, each TBI presents with individual and unique challenges though there are similarities and common threads regarding assessment and treatment. In the workup and management of such patients, it is important to understand the underlying pathophysiology and etiology of the disease. In addition, a solid foundation of knowledge concerning the underlying mechanisms of TBI is important to keep in mind in properly managing the patient. This chapter will present the current medical understanding of the diagnosis and workup of pain as well as a summary of some current evidence-based management options for the patient with acute or chronic TBI.

Though much attention has been paid to mild TBI (concussion) research recently and has brought it to the forefront of media and medical attention, individuals often underestimate the prevalence of TBI as a whole worldwide. While most with mild TBI return to their baseline function, many survivors live with significant disabilities resulting in major socioeconomic burden—estimated direct and indirect costs of $76.5 billion in the US alone in 2010 [1, 2]. Re-hospitalization rates after suffering TBI have also been reported to be as high as 35% within 3 years of initial injury [3]. These numbers may even underestimate burden as it excludes those who do not

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seek medical care or who serve in the military, where the TBI burden is quite high. Adding to the medical complexity of TBI, the often difficult and expensive nature of pain management [4], it becomes clear the necessity to obtain knowledge in these areas to best serve our patients.

29.2 Pathophysiology

Before we can understand the workup and management of pain in the acute and chronic TBI populations, it is important to understand the underlying pathophysiology of the disease process as current clinical practices center around the underlying mechanisms. The pathophysiology of TBI involves two distinct but related processes—the primary and secondary brain injuries. Primary brain injury occurs at the time of trauma and is related to the external mechanical forces transmitted to the intracranial contents (Fig. 29.1). Secondary brain injury is a cascade of molecular processes initiated at the time of the initial injury and can continue for hours to days afterward.

Common etiologies of primary brain injury include direct impact; rapid acceleration/deceleration (the well-known coup countrecoup injury); and, more commonly seen in the military, penetrating injuries and blast waves. Within primary brain injury, there can be several types of pathology seen with the most common being focal cerebral contusions. Due to the location in relation to the basal skull, the most susceptible areas are the basal frontal and temporal areas. Intraparenchymal hematoma can results from merging of cerebral contusions or severe injury resulting in disruption of intraparenchymal blood vessels. Diffuse axonal injury (DAI) has more recently been described due to shearing forces

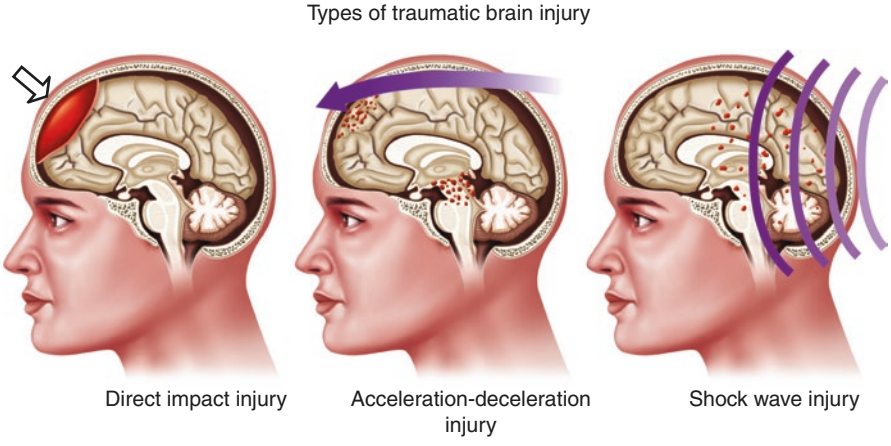

Fig. 29.1 Types of traumatic brain injury

resulting in multiple small lesions seen within white matter tracts, particularly in the gray-white junction of the hemispheres and in the corpus callosum and/or midbrain [5]. DAI has been associated with profound coma and poor outcome and is more readily evaluated via magnetic resonance image (MRI) than computed tomography (CT).

Intra-cranial hematomas can also be seen and classified based upon the location of the bleeding and are the primary reason for urgent CT evaluation in individuals with stroke or suspected bleeding. Epidural hematomas, frequently due to torn dural vessels, are associated with skull fractures and are lenticular shaped on CT. Subdural hematomas result from damage to bridging veins, are crescent shaped, and are more often associated with underlying cerebral injury. Subarachnoid hemorrhage is often seen with disruption of the small pial vessels and in the sylvian fissures or interpeduncular cisterns. Finally, intraventricular hemorrhages are believed to result from tearing of subependymal veins or extension from intraparenchymal or subarachnoid hemorrhages [6].

Secondary brain injury has several mechanisms combine to result in neuronal cell death, cerebral edema and increased intracranial pressure, and can further exacerbate the initial brain injury. It can also have more systemic effects such as hypotension and electrolyte imbalances (particularly hyponatremia) [7]. Despite several pre-clinical trials aimed at targeting the various pathways of cellular injury into developing neuroprotective treatments, none have shown clear benefit. The particular mechanisms involved in secondary brain injury, which share many features of ischemic strokes, include the following [8–14]:

- Neurotransmitter-mediated excitotoxicity causing glutamate and free-radical injury to cell membranes
- Electrolyte imbalances (iron release leads to increased intracellular calcium in particular)
- Mitochondrial dysfunction resulting in release of catabolic enzymes and cessation of bioenergetic and redox functions leading to cell death
- Pro-inflammatory response
- Apoptosis
- Vasospasm, focal microvascular occlusion, and vascular injury

To be considered along with the actual insult, one must consider other medical comorbidities associated with TBI. Up to 35% of TBI patients have extra-cranial injuries as well which can serve to further worsen the brain injury due to blood loss, hypoxia, or other medical complications [9]. Early seizures, late seizures, or epilepsy can result due to increased intracellular calcium leading to excitotoxic damage, neuronal death, and glial scarring which has been demonstrated in animal studies [15]. Acute TBI can also produce coagulopathy via systemic release of tissue factor and brain phospholipids resulting in intravascular coagulation and consumptive coagulopathy [16]. Finally, one can see hyponatremia following TBI due to either syndrome of inappropriate antidiuretic hormone secretion (SIADH) or cerebral salt wasting syndrome (CSWS).

A final consideration in pathophysiology of TBI is paroxysmal sympathetic hyperactivity (PSH), which can occur in patients with moderate to severe TBI due to dysregulation of autonomic function. Clinical manifestations include recurrent, abrupt-onset episodes of excessive sympathetic activity—tachycardia, hypertension, tachypnea, diaphoresis, posturing—that resolve either spontaneously or with abortive medications. While commonly due to pulmonary embolus; sepsis; and elevated intracranial pressure, acute painful episodes can both cause symptoms similar to PSH and induce episodes of PSH. Should this arise, one must consider underlying sources of pain including fracture, spasticity, cholelithiasis, nephrolithiasis, thrombus, nephrolithiasis, constipation, and urinary retention or infection [17]. While the pathophysiology of PSH is incompletely known, it is suspect acute brain injury results in a disconnection between cortical inhibitory areas and lower sympathetic centers in the hypothalamus, brainstem, and spinal cord [15].

29.3 Risk Factors

Risk factors for initial TBI include adults greater than 75-years-old, children ages 0–4 years, young adults aged 15–24 years old, male gender, lower socioeconomic status, alcohol or drug use, and underlying psychiatric or cognitive disorders [18–20]. Following a very similar trend, risk for rehospitalization after suffering a TBI include the following: male gender, older age, greater severity of initial TBI, unknown mechanism of injury, and psychiatric comorbidities [3].

We will also briefly discuss outcome of TBI as it frequently will be asked of multiple providers in the acute setting though it should be noted prognosis is difficult to predict and depends on multiple factors including severity of TBI, medical complications, secondary brain insults, and baseline patient characteristics. While none of the following risk factors can be used in isolation to predict outcome, each has been demonstrated to predict negative outcome [21]:

- GCS score at presentation (especially the GCS motor score)
- Full Outline of UnResponsiveness (FOUR) score
- Pupillary function
- Age
- Associated extracranial injuries and complications
- Hypotension
- Hypoxemia
- Pyrexia
- Elevated intracranial pressure
- Reduced cerebral perfusion pressure
- Bleeding diathesis (low platelet count, abnormal coagulation parameters)
- CT findings: High-grade subarachnoid hemorrhage, cisternal effacement, midline shift, leukoaraiosis
- MRI findings: Presence of diffuse axonal injury and/or brainstem injury

29.4 Diagnosis

While initial diagnostics does not typically fall within the realm of the inpatient pain provider, understanding the diagnostic criteria may help with developing and understanding of treatment algorithms. TBI is categorized in terms of clinical severity, mechanism of injury, and primary underlying pathophysiology. Initial diagnostics can have prognostic implications and having an appreciation of such will aid in the working with the multi-disciplinary teams that are continuously involved in treating TBI. In looking at diagnostic algorithms, there are several times during treatment that will establish the treatment course and develop a long-term treatment strategy.

Initially developed by Teasdale and Jennett in 1974 [22], the Glasgow Coma Scale (GCS) has become the most widely used clinical measure for severity of injury with multiple studies demonstrating a fairly high degree of reproducibility among differing providers. The GCS is rated on a 3–15 scale with sub-scores of motor response (6 points), vocal response (5 points), and eye opening (4 points). Adding the sub-scores gives a total score with 13–15 being mild injury, 9–12 moderate injury, and 3–8 severe injury. Limitations to GCS include amount of medical sedation and paralysis, endotracheal intubation, and intoxication which tend to be more prominent in individuals with lower GCS scores. Initial GCS scores have been used in multiple studies correlating GCS with outcome demonstrating if the initial GCS is obtained without confounding factors, patients with initial GCS less than 8 have demonstrated 30% mortality in cohort studies. Other studies have demonstrated 30–65% of patients with severe TBI will regain independence though functional recovery can take up to 6–12 months [23, 24]. A second, commonly-used scoring system is the 10-level Rancho Los Amigos Scale for assessing TBI recovery. This scale is a 10-point scale ranging in behaviors from no response and total assistance at level 0 to purposeful, appropriate behaviors for level 10. The most meaningful transition occurs between levels 4 through 6 where patients go from confused and agitated with maximal assistance at level 4 to confused and appropriate with moderate assistance at level 6. Purposeful and appropriate behavior and cognition with stand-by assistance finally comes at level 8.

While a good tool for moderate to severe TBI, the GCS is not diagnostic for TBI and will often return normal in individuals with mild TBI in particular. To this end, other tests have been developed to diagnose TBI though many of these rely on patient-reported symptoms. In addition to the GCS, if an individual has no loss of consciousness or loss for less than 30 min with memory loss less than 24 h, it can be considered a mild TBI (concussion). A moderate TBI then has loss of consciousness between 30 min and 24 h or memory loss from 24 h to 7 days. Severe TBI is indicated if the patient loses consciousness for more than 24 h or memory loss persists greater than 7 days. Even in the absence of the above symptoms, individuals can suffer from a TBI with lesser symptoms and no loss of consciousness (as seen frequently in athletics). Symptoms in this cohort consist of inability to maintain a coherent stream of thought, a disturbance of awareness with heightened distractibility, and an inability to carry around goal-directed movements. This may result in

symptoms such as headache, visual disturbances, dizziness, nausea, balance deficit, confusion, tinnitus, difficulty concentrating, or light sensitivity. Given the often-difficult nature of diagnosing a concussion, it can be helpful to suspect TBI is present until it can be ruled out. This author's personal approach in athletic sideline coverage is to err on the side of caution and remove athletes if any of the above symptoms or present or the behavior of the athlete leads us to believe a concussion is likely.

Neuroimaging is frequently used in the diagnosis of TBI as well though is it not 100% sensitive as often low-grade TBI's will show no abnormalities even on MRI. While significant time could be spent in discussing the neuroimaging of TBI, it is beyond the scope of this chapter and we will focus on the key points therein. In the acute setting, CT is the preferred imaging modality for expedient evaluation of pathology that could indicate potentially lifesaving neurosurgical intervention. Non-contrast CT is useful in detecting skull fractures, intracranial hematomas, and cerebral edemas and should be obtained in all individuals with GCS of 14 or lower and when intracranial-hemorrhage is suspected. Follow-up CT is recommended in the case of clinical deterioration as evolution of findings may indicate alternative treatment approach should be pursued. If hematoma is present, some advocate for repeat imaging in patients with low GCS. While nearly 100% sensitive in detecting hemorrhage, CT is not reliable in detecting DAI. The most common MRI finding in DAI is multifocal areas of abnormal bright T-2 signal in the grey-white junction, the corpus collosum, or the brainstem [25].

29.5 Treatment

The following discussion of the treatment of pain in TBI will be broken down into several categories. These include non-pharmacological management, pharmacological management, and interventions. We will then discuss chronic pain briefly noting prevention of chronic pain begins with the treatment of acute pain. Each of these treatments has inherent advantages and disadvantages and some patients may respond appropriately to one and not the other. One will also need to monitor for side effects and may need to take additional precautions in the TBI population.

29.5.1 Non-pharmacologic

Patients with moderate to severe TBI are frequently admitted to intensive care units or, if on the general floor, have diminished functional abilities. While pain control is often sought initially through medications, I start this section with non-pharmacologic therapy to stress the importance for long-term benefit. Implementation of respiratory, physical, and occupational therapy into the multi-disciplinary team has become more commonplace as we have begun to recognize the long-term physical

impairments of ICU patients. Particularly while on mechanical ventilation, patients can experience significant muscle weakness and functional decline. Therapists can design programs to aid in range of motion, ventilation, positioning, and can provide manual techniques to help with sputum accumulation. Early therapy in the ICU has been demonstrated to reduce the overall ICU and hospital length of stay, prevent ICU-related complications, improve functional and quality of life in the long-term, and improve mortality rates [26].

29.5.2 Pharmacologic

Prior to discussing medications, there are some general principles to remember. Many patients with TBI are abnormally sensitive to or intolerant of medication side effects. There exist no randomized, controlled clinical trials to support using medications in this population so extreme care must be taken. To ensure safely, start with low dosages and increase very gradually to assess side effects and drug efficacy. In order to ensure efficacy, give full trials of medications with adequate dosing prior to discontinuing. Continue to monitor patients closely for side effects, especially in non-verbal TBI patients. And seek advice from individuals around most—nursing staff, family, friends—to evaluate a medication's effectiveness as cognitive deficits may hinder their ability to accurately pain.

In the acute phase of moderate to severe TBI, effective analgesia is imperative as pain can often go unrecognized. Fentanyl is commonly used in this setting compared to morphine to minimize hemodynamic instability. Utilizing this analgesic-based sedation, one can often avoid use of a sedative though use of Propofol is common given its short duration of action and efficacy in decreasing cerebral metabolic demand and ICP. While opioids can frequently be given in TBI, it is important to continue to use analgesics from differing classes in order to optimize analgesia. It is also essential to consider the underlying etiology of the pain as differing pain generators can result in differing types of pain. While opioids tend to be very beneficial medications for acute pain, many patients also suffer from headaches and/or neuropathic pain and should be treated accordingly. In these scenarios, recommendations would be to utilize medications that can be easily titrated and have limited mental side effects. One such option would be gabapentin for neuropathic pain though mental fogginess can occur. One must also balance side effect profiles of the chosen medications. Patients with TBI can have sleep disturbances and medications should also be chosen here to assist with management of pain while limiting sleep disturbances. If the above patient with neuropathic pain also has difficulty initiating sleep at night, gabapentin would become the first treatment recommendation due to the side effect profile of sedation.

As previously mentioned, patients often have extra-cranial pathology which can result in significant pain. For example, one of the most common causes of TBI is motor vehicle accidents. It is easy to imagine a patient with TBI in addition to whiplash injury, fractured ribs from a seatbelt, fractured wrist, abdominal pain due to lap

belt trauma, etc. each of which can cause significant pain of themselves. In these patients, one must often provide invasive means of pain control whether this be intercostal nerve blocks for fractured ribs, regional anesthesia pre-operatively, or systemic intravenous opioids. Important in this decision in addition to the actual procedures performed is the informed consent. There have been many ethical debates surrounding obtaining consent for procedures in cognitively impaired individuals and I would suggest each pain provider be familiar with the hospital practices. One exception to obtaining consent occurs when an emergent, life-saving procedure is required or delaying the procedure to obtain consent would result in serious harm to the patient.

Paroxysmal sympathetic hyperactivity (PSH), though not a pain condition itself, bears special consideration to the pain provider. Initial management is via supportive measures, but many have found benefit of using pain medications in abortive and preventative manners should pharmacotherapy be required. Unfortunately, most evidence supporting pharmacotherapy for PSH is based on case series and anecdotal evidence. Clonidine and beta blockers have been demonstrated to be effective as both abortive and preventive drugs. For episodes lasting longer than a few minutes, intravenous morphine (starting dose of 2 mg) can be used as abortive with gabapentin (starting at 100–300 mg 3× daily), non-cardioselective beta blocker (e.g., propranolol starting dose 10 mg 3× daily), and/or clonidine (starting dose 0.1 mg twice daily) used as preventive. With the above starting doses, patients must be continually monitored as frequent dose titrations are often required though hypotension may be a dose-limiting side effect. Adjuncts to this regimen include benzodiazepines and baclofen. Should a patient exhibit posturing, dantrolene can be considered. Notable medications to avoid include dopamine antagonist drugs such as typical and atypical antipsychotics and metoclopramide [21].

29.5.3 Mild TPI/Concussion

Headaches are frequently seen in both the acute sub subacute phase of mild TBI. If mild TBI is suspected, brain rest is the current treatment regimen to aid in recovery. This includes avoidance of television, telephone screens, video games, bright lights, physical and mental stimulation, and even school work. Pain control should be achieved with over-the-counter medications such as acetaminophen. Avoidance of opioids and other medications that can cloud mental status or neurological examination is advised. In fact, overuse of analgesics following mild TBI can exacerbate injury-related headaches or make them chronic. Other medications that have been used with success for post-concussive headaches include beta-blockers, calcium channel blockers, valproic acid, topiramate, triptans, dihydroergotamine, and gabapentin though most evidence is either anecdotal or limited to case series.

Injection therapy has also been used in a lesser degree for the treatment of post-concussive headaches. Many providers have had success with trial of dry needling or trigger point injections. There have been multiple case series demonstrating

occipital neuralgia in the post-concussive patients as well as whiplash cases. There can also be some symptom overlap including nausea, dizziness, and photosensitivity. Though limited to case series, one could consider a trial of greater and lesser occipital nerve blocks in work-up for potential radiofrequency ablation. Case series have also reported benefit of botulinum toxin injection for post-concussive headache.

29.5.4 Chronic Pain

Chronic pain is common after TBI and while beyond the true scope of this chapter, pain providers should counsel patients prior to discharge to ensure best long-term care for their patients. The first choice for pain management in chronic TBI is non-pharmacologic therapy as many pain medications can alter mental status. We can use many of the same principles in treating chronic TBI patients as patients without TBI in this regard. Patient's should be encouraged to get regular exercise which can be beneficial for both the mind and body. Avoiding stressful situations and maintaining sleep hygiene is also important. Substances to avoid include caffeine, alcohol, tobacco products, and any food that can trigger headaches, should they suffer from food-related headaches. If cognition allows, regular participation with psychotherapy should also be encouraged as these individuals can have difficulty with coping and even post-traumatic stress disorder given the traumatic nature of their injury. Alternative treatments with less evidence include acupuncture, Tai Chi, and massage therapy.

In soldiers, chronic pain is common following TBI (specifically with blast-related TBI) and polytrauma, particularly headaches. A polytrauma triad of post-concussive syndrome, PTSD, and chronic pain has been described with only 3.5% of all veterans having none of the above symptoms and 42.1% exhibiting all three [27]. The most common locations in chronic TBI for pain were low back and headaches. Visual and auditory deficits can also result due to blast injury. This population will need a multidisciplinary team consisting of pain provider, psychology and/or psychiatry, and a primary care provider at minimum though cognitive sequelae would benefit from addition of a physical medicine and rehabilitation specialist.

29.6 Pain Assessment Tools

Assessing pain in the inpatient setting is a difficult endeavor in most circumstances notwithstanding the addition of cognitive impairment that can be present in TBI. Should a patient have minimal cognitive impairment, one could implement a variety of pain scales of which the most common are pain intensity are verbal rating scale, numeric rating scale, and visual analog scale. Throughout our medical careers, we get extensive experience with these scales so we will turn our focus onto the more challenging of circumstances that surround TBI. As

mentioned previously, up to 35% of patients with TBI have extra-cranial trauma that can be the source of significant patient pain. In patients with altered consciousness, we are often not afforded the liberty of asking where pain is located or how severe the pain may be. We must also consider that a significant proportion of patients with TBI are either very young or elderly which can also compromise pain assessment.

In the cognitively impaired cohort, it has been demonstrated that visual rating scale produces the least "failure" responses while the visual analog scale has the highest number of patients who fail to report significant pain [28]. Some research has suggested that use of behavior pain may be preferable even in patients who are able to communicate as pain intensity is underreported despite indications of pain relief and lesser pain behaviors [29]. Other pain assessment tools that have been utilized include Wong-Baker FACES, Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale, Certified Nursing Assistant tool, Elderly Pain caring Assessment, and the Pain Assessment in Advanced Dementia Scale. While all different in their actual make-up, each relies upon facial expression, eye opening, frowning, lip changes, clear movements of the extremities, neck stiffness, and sighing or moaning. Many ICU's have begun a trial of pain management in non-communicative individuals when signs of pain including hypertension, elevated heart rate, or signs of agitation. Vital sign changes alone however cannot be utilized as a sole indicator of pain or lack of pain though one often does see changes with acute pain. It must not be understated that a team-based approach to patient care in these often-complex patients be undertaken to properly assess the patient and avoid undertreating pain.

29.7 Challenges in Management of Pain While in the Hospital

Managing pain in the hospital is an inherently complex task. As previously outlined in this chapter, patients with TBI present a new challenge to the pain provider and the care team as a whole. Mismanagement of these patients can have detrimental effects, not only in the realm of chronic pain, but within the hospital stay itself. Challenges in the management of TBI patients stem from the TBI itself in patients can have functional and cognitive dysfunctions that limit the expression of pain as well as the assessment of pain. Patients may also have extra-cranial pathology causing significant pain and distress. Adding in the multi-disciplinary nature of treating TBI where multiple care providers are nearly always involved adds a team dynamic that can, at times, prove challenging though done correctly, can greatly improve patient outcomes. Psychosocial issues must also be considered as patients with traumatic nature to their brain injury can suffer from PTSD. Caregiver burden upon discharge and potential caregivers should be involved early in care to increase their knowledge and improve patient care upon discharge.

While every TBI is unique in the location of brain damaged and the amount of damage inflicted, there are some general treatment guidelines that we defined above. In the severely cognitive impaired when the patient is intubated, sedation is often sought through the use of IV opioid analgesics, termed analgosedation. However, in the lesser impaired, opioids may not be the best option as they can lead to mental cloudiness in some which should be avoided if possible in the TBI population. This brings another treatment complication as many medications used in the treatment of pain can affect mentation. TBI itself can also be a source of neuropathic pain and, if possible, medications choices should be tailed to best suit the clinical scenario. This may indicate a procedural modality is best for the patients and the consent process must be appropriately done per respective hospital regulations. We also briefly discussed mild TBI (concussion) pain management. If possible, over-the-counter analgesics such as acetaminophen should be attempted for headache management.

Within the management of these patients, TBI sequelae must also be considered. Paroxysmal sympathetic hyperactivity was briefly mentioned above as pain medications are often used in both prevention and treatment. Other medical complications seen in acute TBI include coagulopathy, intracranial hypo- or hyper-tension, hydrocephalus, hypotension, electrolyte balance (most notable is hyponatremia due to cerebral salt wasting or symptom of inappropriate antidiuretic hormone), posttraumatic seizures, DVT and pressure sores due to immobility, muscle spasticity, agitation, and gastrointestinal and genitourinary complications amongst the host of other medical complications that are present in this patient population.

29.8 Management of Pain in the Inpatient Setting

Prior to any pharmacological or invasive intervention, conservative approaches should be exhaustive if possible. We must also realize that certain clinical scenarios will bypass this approach though in this case, non-pharmacologic and interventional approaches should be used to adjunct treatment. Physical therapy, cognitive behavioral therapy, yoga, acupuncture, and other forms of conservative traditional pain management techniques all have their place though not all hospital settings have these available. One difficulty is knowing how to accurately assess pain in cognitively impaired individual and knowing when to escalate to more pharmacological and invasive based techniques in order to limit any consequences of untreated pain in their patient. Patients with TBI often are treated in a heavily multi-disciplinary fashion and working with our colleagues is likely the best way to assess pain and response to treatments.

In the treatment of TBI, there exist few definitive treatment algorithms yet there are key elements to consider. Though not tools often used to pain providers, medications to avoid include clonidine, trazodone, phenytoin, phenobarbital, diazepam, haloperidol, and thioridazine as these have been demonstrated to impede TBI recovery [30]. It should also be noted that amantadine has been demonstrated to improve cognitive recovery if given in the acute setting [21]. While we could spend significant

time evaluating differing classes of medications for treatment of TBI agitation, psychosis, attention, etc. that is beyond the scope of this chapter.

29.9 Discharge Plan for Pain Management

Once the inpatient with TBI is ready to be discharged, follow up clinical visits become an important treatment modality. Lack of optimal discharge planning can have far-reaching negative consequences for these complex patients. Discharge planning requires a multi-disciplinary approach similar to the inpatient care team and we often rely on assessment by speech, occupational, and physical therapy to aid in the best placement for patients—home, subacute rehabilitation facility, or inpatient rehabilitation unit. Regarding the TBI itself, most individuals would benefit from the care of a TBI specialist, often general physical medicine and rehabilitation though some areas may provide clinicians with additional training in TBI care. In the most severe TBI's, some locations even provide inpatient-type specialty care in TBI. In cases of mild TBI or concussion, a wider variety of providers are adept at providing care including the primary care provider, physical medicine and rehabilitation, or sports medicine. I would encourage all providers to be familiar with the individuals in their area who have developed an expertise in managing chronic TBI for such occasions. Patient's presenting to the hospital with chronic TBI symptoms should be encouraged to establish care with, at minimum, primary care and physical medicine and rehabilitation providers upon discharge. In all scenarios, one should seek to involve the family, caregivers, or loved ones in discharge planning as many patients with TBI will need some form of assistance upon discharge.

As mentioned previously, over one third of all acute TBI patients have extracranial pathology. While we cannot cover all possibilities of necessary follow up, one must consider follow up based on the presenting symptoms and other pathology found during the hospitalization. Hospital pain follow up should also be based on the presenting symptoms. For instance, patients with headaches may best be served by seeing neurology who are familiar with both TBI and headache management. Pain due to trauma are likely best served in a multi-disciplinary fashion to include trauma surgery, pain management specialist, physical therapy, and occupational therapy. Regarding the latter of these, given the functional limitations often seen following TBI, I would encourage all providers to strongly consider outpatient physical therapy and occupational therapy even should the patient not qualify for inpatient rehabilitation after acute TBI hospitalization. Cognitive impairment can leave individuals with deficits that affect their mobility and ability to perform even the simplest of activities of daily living which can be greatly aided by therapy services. While caring for patients with TBI can be challenging, working in a team to care for these individuals and watch their improvement can be very satisfying on a personal and intellectual level.

29.10 Summary

- Workup of the inpatient with any level of TBI-related pain must begin with a thorough history and physical exam.
- Investigations including imaging and labs should be performed based on the acuity of the situation and the inciting traumatic event
- Patients receiving treatment should be aware of all benefits, alternatives, and risks to which ever treatment modality is being considered. The goals of treatment should be reviewed with the patient. If the patient is cognitively impaired, the provider should be familiar with their respective hospital policy regarding consent to non-emergent treatment.
- The treatment plan should be discussed with the entire treatment team and should be based on sound evidence-based data and established clinical practice.
- Conservative non-pharmacological treatment options should be the forefront of any treatment plan. Even in the intubated and sedated patients physical, occupational, and respiratory therapy have their place in the treatment algorithm
- Pharmacological management choice should be based on patient preference, medical comorbidities, availability, cost, and side effect profile.
- More invasive techniques should be considered in patients whose pain is refractory to more conservative measure or when the benefit to invasive procedure outweighs the risk involved with systemic medications
- Adequate pain assessment is an important tool when deciding on treatment modality and treatment necessity. While often difficult in cognitively impaired patients, there are scales that can be used in addition to care-team reported response to treatment.

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Chapter 30
Informed Consent

Elizabeth Wilson and Kristopher Schroeder

30.1 Introduction

Obtaining procedural consent is a critical component of developing a trusting and collaborative relationship with patients. This process provides the physician with the opportunity to present an insightful anesthetic or analgesic plan to patients in an empathic manner that reaffirms the patient's central role as collaborator in their own healthcare. Properly done, this process may result in improved patient outcomes, an improved perception of the physician's skill and caring and reduce the risk of significant litigation [1]. Obtaining consent for regional anesthesia or other pain-related procedures should not differ in any substantial way from any other procedure. However, there are a number of potential ethical and medicolegal confounders that Anesthesiologists might encounter in the course of obtaining informed consent for regional anesthesia procedures.

Anesthesiologists are frequently faced with the difficult task of providing analgesia for patients with acute/chronic pain or recovering from a surgical procedure. Unfortunately, these patients often possess attributes that may complicate obtaining consent or otherwise make these patients less capable of participating in the consent process. These patients frequently present for surgery with significant anxiety and there may be significant reluctance on the part of providers to increase patient anxiety further with a discussion of serious but rare complications.

Complicating matters further, Anesthesiologists often do not have the opportunity to spend abundant time with patients to gain an appropriate or in-depth understanding of these patient's values, beliefs or cultural background that might influence their decision making process. Even interactions with family or other potential surrogate decision makers are generally fairly limited in the course of the provision of

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standard anesthesia care. These complicating factors can collaborate to create general unease among anesthesia providers and potentially result in situations where the provision of analgesia is hampered by a lack of consent clarity. In particular, the impact of pain, medications, previous analgesic preference determinations or advanced directives can create a situation where the ethical path to obtain consent and provide analgesia is unclear [2]. Even what information must be disclosed has regional variability with individual states possessing the ability to determine the standard of material risk disclosure (i.e. provider versus patient standard) [3].

Fortunately, there are concepts and legal precedents that can guide providers confronted with these types of ethical conundrums. In addition, understanding the value of patient autonomy, building a strong patient-physician relationship and documenting efforts at providing a thoughtful provision of analgesia will generally maximize outcomes and limit liability.

30.2 Challenging Cases

- ***Case 1: A 29-year-old pregnant woman arrives at the labor and delivery suite with a birth plan that specifically refuses the use of epidural analgesia. As labor progresses, the patient experiences pain that requires the administration of systemic opioids. Despite opioid administration, the patient continues to experience significant and intolerable pain and she adamantly requests an epidural be inserted as expeditiously as possible.***
- ***Case 2: A 54-year-old man presents for open colectomy for which the surgical team has requested the preoperative placement of an epidural catheter. Following a thorough description of risks, benefits and alternatives, the patient prefers to avoid regional anesthesia and attempt to manage postoperative pain with opioid analgesics. Following an uneventful surgical course, postoperative pain control proves challenging and the patient now requests that an epidural catheter be inserted.***
- ***Case 3: A 33-year-old man presents for laparoscopic appendectomy that requires conversion to an open procedure in the operating room. There was no preoperative discussion of potential regional anesthesia procedures. While in the recovery room, the surgical team and patient now request that an epidural catheter be inserted.***
- ***Case 4: A 22-year-old woman remains intubated and sedated following bilateral lung transplant for cystic fibrosis. No preoperative discussion of epidural analgesia was completed. The surgical team now requests epidural analgesia to facilitate extubation.***
- ***Case 5: An 87-year-old man with severe Alzheimer's disease and an activated power of attorney presents for laparoscopic colectomy. The surgical team requests a preoperative quadratus lumborum block.***

- ***Case 6: The trauma service consults the acute pain service for a 39-year-old man with multiple rib fractures sustained following a motor vehicle collision. The patient is intubated, sedated and without immediately available family members.***

In each of these cases, there are significant issues related to the acquisition of adequate informed consent. Various questions that might be considered include the immutability of birth plans or advanced directives, the ability of pain and analgesics to impair decision making capacity, the role of surrogate decision makers in clarifying the wishes of sedated or anesthetized patients and how to balance the known and the unknown (i.e. risks of systemic analgesics and epidural analgesia with unknown risks/efficacy of novel fascial plane blocks). The intention of the following chapter is to provide the reader with the tools required to adequately address these questions and effectively care for these postoperative patients.

30.3 Legal History

The term informed consent was born in the United States judiciary system and addressed the liability of professionals as agents of disclosure [4]. Over the past century, several landmark cases have molded the legal definition of informed consent.

In 1914, Schloendorff v. Society of NY served as one of the earliest court decisions to tackle the idea of informed consent by using battery as the claim in which a physician consented a patient for exam under anesthesia but instead removed a fibroid tumor. In the decision, Justice Benjamin Cardozo wrote, "Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages" (Schloendorff v. Society of New York Hospital, 105 NE 92 (NY 1914)). In this decision, an exception was made for cases of emergency where the patient is unconscious and where it is necessary to operate before consent can be obtained.

In 1957, the second landmark case addressed the duty of disclosure with respect to informed consent. In Salgo v. Leland, a patient suffered paralysis after an aortogram which was a risk that was never discussed. The ruling stated that "A physician violates his duty to his patient and subjects himself to liability if he withholds any facts which are necessary to form the basis of an intelligent consent by the patient to the proposed treatment" and "Likewise the physician may not minimize the known dangers of a procedure or operation in order to induce his patient's consent" (Salgo, 317 P 2d 170, 181 (Cal Ct App 1957)). Thus, if a physician failed to provide comprehensive disclosure, he or she could be considered negligent. However, comprehensive disclosure was not clearly defined.

Additional case law in 1960 and 1972 served to define the standard of disclosure. The first case Natanson v Kline took place in Kansas and involved a woman with breast cancer who sued the radiologist for administering too much radiation and suffered disabling burns despite being told there were no risks associated with this treatment. The court held the medical profession responsible for a standard of disclosure of risks that a reasonable practitioner would provide a patient in hopes of "balancing patient rights of self-determination with respect for the medical community's wisdom and tradition". This decision became known as the physician standard of disclosure (Natanson v. Kline 350 P.2d 1093 (Kansas 1960)). Twelve years later, a second case addressed disclosure standards. Canterbury v Spence (1972) involved a 19-year-old with back pain who underwent laminectomy and was never informed of the risk of paralysis. The court's decision stated "the adequacy of the physician's disclosures to the patient must be measured by the patient's need and that need is the information material to the decision so that all risks potentially affecting the decision are unmasked". A risk was determined "material" when a reasonable person, in what the physician knows or should know to be the patient's position, would be likely to attach significance to the risk in deciding whether or not to forgo proposed therapy. (Canterbury v Spence 464 F. 2d 772–786 (D.C. Cir 1972)) The impact of this case made it clear a patient's right of self-decision shapes the boundaries of the duty to reveal. This change in disclosure standard was said to increase respect for patient autonomy and became known as the patient standard of disclosure.

Today, there are essentially two standards of disclosure for consent: the physician standard and patient standard. In the United States, the standard of disclosure for informed consent varies from state to state and this has been shown to have legal implications for practicing physicians. A study published in 2007 by Studdert et al, analyzed 714 jury verdicts in informed consent (mostly failure to disclose surgical risks) that were tried in 25 states from 1985 to 2002. They found that the odds of a verdict for plaintiffs were nearly twice as high in states with the patient standard vs. professional standard for informed consent disclosure. The study showed a clear difference in litigation outcomes based on disclosure standards and highlighted three major implications. First, physicians in states that held a reasonable patient-standard incur greater exposure to liability. Second, cases with similar facts may be decided differently based on the state in which they are tried. Third, these findings suggest a discrepancy between customary medical practice or professional standard and the patients' expectations about risk disclosure [5]. Therefore, it is imperative that practicing physicians understand the legal climate in which they practice.

30.3.1 Ethical and Legal Responsibility

From a legal standpoint, informed consent serves to protect patient autonomy. From an ethical standpoint, physicians have a moral obligation to protect patient health by providing care that upholds the physician-patient partnership and identifies the best

treatment for each patient based on a patient's preference while balancing risks and benefits. Certainly, the extensive training received by physicians allows them to council and provide advice regarding healthcare decisions. This interaction is core to collaborative healthcare decision making and the physician should view themselves as an advisor to the patient in these matters. However, physicians are obligated to provide information on risk and alternative therapies and must respect the decision made by their patients.

30.4 Consent

A contemporary understanding of consent for anesthesia procedures requires a thorough understanding of procedural and content requirements. Previously published literature has divided the elements of informed consent into threshold elements (competence, capacity, voluntariness), information elements (disclosure, recommendation, understanding) and consent elements (decision, authorization) [2, 4].

In practice, healthcare providers must first assess the patient's ability to make a decision relevant to the proposed medical intervention. A more thorough discussion of capacity including required components and various assessment tools is to follow. Assuming adequate patient capacity for decision making exists, patients must understand that this decision is one that they must make, and that the role of the healthcare provider is to provide facts and guidance but not to ultimately make the healthcare plan decision.

With regard to disclosure of risks, Anesthesiologists have proven difficulties balancing patients' desires for obtaining a solid foundation of pertinent medical information and avoiding unnecessarily frightening patients [6–8]. In fact, a 2010 study of UK Anaesthesiologists reported that 22% believed that obtaining consent was unnecessary and that 55% believed that the consent process was often inappropriate given that patients recall little of the information provided to him and that the information presented to them might result in unnecessary worry or confusion. In this study, a majority of Anesthesiologists reported that risks that occurred greater than 1% of the time should be disclosed. However, <50% believe that serious and major risks with an incidence of 1:10,000 should be routinely disclosed. Of note, surgeons and Anesthesiologists reported similar risk disclosure thresholds [9]. The rate at which patients recall Anesthesia consent information is generally poor and variably and inconsistently impacted by method of risk disclosure. In a study by Zarnegar, 98% of patients recalled meeting their Anesthesiologist and 91% believed that the consent process was adequate. However, 45% of patients were unable to recall a single risk of interscalene blockade and only 20% could recall two or more risks [10]. Despite generally poor patient recall, risk disclosure and documentation of this discussion remains vitally important.

In a study by Brull that specifically evaluated risk disclosure prior to regional anesthesia, 74% of respondents reported routinely disclosing risks of regional anesthesia procedures to patients in order to facilitate the ability to make an informed

decision while 26% reported that they do so for purely medico-legal reasons. In this survey study, it was also reported that Anesthesia providers are generally effective at disclosing the risk of common and minor adverse events. For example, the risk of postdural puncture headache following spinal anesthesia was disclosed frequently. However, the risk of serious adverse events following spinal anesthesia including death, paralysis and respiratory arrest were disclosed significantly less frequently. Finally, the authors found that when risks were disclosed that they did not accurately reflect current risk estimates. Proposed reasons for this discrepancy were that providers were either unaware of contemporary risk estimates or felt that the literature was flawed [11, 12]. It is also certainly possible that providers tailor risk estimate to account for their personal experience with procedure performance and the patient's risk factor profile.

Despite poor patient recall and a lack of Anesthesiologist enthusiasm for risk disclosure, studies have consistently demonstrated that patients desire a fairly complete description of potential procedural risks and relevant alternatives [13–15]. In the obstetric population, multiple trials have demonstrated that patients desire significant information regarding potential risks of neuraxial anesthesia. In one study of obstetric patients, 70% indicated that they preferred disclosure of all risks (minor and rare/serious) in the course of a consent discussion [16]. In addition, it appears that patient's desire for risk disclosure information is increasing. A 2016 study demonstrated a significant increase in parturient interest in disclosure of rare but serious risks of epidural anesthesia between 2010 and 2016 (16–33%) [17]. There may also be cultural differences with regard to desire for risk disclosure with previous research demonstrating that patients in the United States have a greater desire for an unabridged risk disclosure [15].

While one needs to be careful to not make assumptions regarding desired risk disclosure, previous research has demonstrated that disclosure of the risk of death is generally most important to patients and is impacted by educational level [18]. In certain circumstances, it may be incredibly important to a specific patient to discuss the incidence of certain risks that may be of little consequence to others. For example, the risk of a permanent 10% decrease in quadriceps strength may be of much greater significance to a professional athlete than to someone who makes their living via some other profession. In a professional singer, the potential risks of a spinal anesthetic may be greatly outweighed by the risks of vocal cord injury with endotracheal intubation. It is therefore vitally important to understand the values of your patient when attempting risk disclosure.

In the course of risk disclosure, it is also important to acknowledge and disclose that there are certainly risks associated with the avoidance of regional anesthesia. Poorly controlled pain can reduce the quality of life and impair sleep [19]. It is not a profound leap to consider that poorly controlled pain might impact physical function and limit patient's ability to fully participate in physical therapy. For certain procedures (i.e. joint arthroplasty), this impaired ability to participate in physical therapy might produce a significant impact on the success of the surgical procedure. Poorly controlled pain might also have profound physiologic impacts where it could produce tachycardia and hypertension. Finally, the impact of poorly controlled

acute pain on the development of chronic pain and opioid abuse disorders is an issue that warrants discussion [20].

Whatever consent discussion does occur, it is imperative that physicians document that a discussion of potential risks, benefits and alternatives has occurred. In addition, a description of the patient's current level of decision-making capacity should also accompany the consent discussion documentation. The nature of this documentation depends on a number of factors but can generally be accomplished via a variety of mechanisms. Documentation of consent discussions in the electronic medical record may be adequate. In other circumstances, an anesthesia or procedure-specific consent form may improve the consent process or the conveyance of information to patients. In large groups or busy practices, the use of standardized check-lists might significantly improve the consistency with which information is delivered [21–24]. A lack of any sort of documentation of the consent process may be utilized as a legal strategy to demonstrate fault if an adverse outcome were to occur following a regional anesthesia procedure. Whatever information conveyance and documentation strategy is utilized, it should be understood that this process does not guarantee absolution from potential litigation if the standard of care is not upheld.

30.5 Competency

Competency is a legal finding and court affirmed. Competency refers to the mental ability and cognitive capabilities required to execute a legally recognized act rationally [25]. Competency proceedings, including guardianship and conservatorship hearings, are conducted to allow the court to determine an individual's mental capacity. If a person is determined to be incompetent, consent must be obtained from a court-appointed guardian.

In patients that are deemed to be incompetent, consent issues become largely irrelevant as it has been pre-determined that the court-appointed guardian is responsible for making decisions on the patient's behalf. Where this situation may become more challenging is if the court-appointed guardian is unable to be contacted. In this scenario, urgent decisions can likely be appropriately made in the patient's best interest while continuing efforts are made to contact the guardian. More elective decisions should be delayed until the guardian is contacted or the court is able to designate an alternate decision-maker. In situations where questions arise, contacting institutional legal consultation is likely appropriate.

30.6 Capacity

Medical decision-making capacity is determined by the clinician and relates to a patient's ability to assimilate information, debate the risks and benefits and communicate a decision. It is important for a capacity assessment to occur every time patients

are presented with consent material. This capacity assessment can be made by any healthcare provider and is generally done informally during the course of conversations with patients. Care must be exercised in a busy practice to not omit this step as many patients possess the ability to mask mental handicaps that can only be uncovered following a thorough discussion and effort to unmask deficiencies. While no foolproof capacity assessment tool is yet available, groups have effectively found a positive correlation between the impressions of healthcare providers, the Standardized Mini-Mental Status Examination (SMMSE) and expert opinion [26]. Other studies have demonstrated that the SMMSE is only useful at either extreme and is inferior in clinical practice to the Aid to Capacity Evaluation (ACE) test [27, 28]. In addition to the SMMSE, there are several tools that have been used to determine capacity, which have mostly been tested in Alzheimer's patients. These tests include the MacArthur Competence Assessment Tool Treatment or MacCAT-T, the Capacity to Consent to Treatment Instrument or CCTI and the Hopkins Competency Assessment test.

In simple terms, patients that possess adequate capacity to make decisions are able to understand the presented information, retain it long enough consider the various risks and benefits and ultimately make a decision regarding the provision of care [1]. Stated another way, capacity represents the ability of a patient to understand, appreciate, reason and make a choice among the options provided for their healthcare [29, 30]. Within this framework, it is important to understand that patient conditions are not static and that various levels of capacity may be required for different decisions. For example, patients with delirium, dementia, pain, anxiety or systemic illnesses may have waxing and waning periods of capacity retention and it is for that reason that capacity assessments should occur prior to each decision [2, 31]. In addition, there may be a higher level of capacity required prior to obtaining consent for an invasive or surgical procedure that what might be required prior to the administration of antibiotic therapy. In situations where capacity assessments may be unclear, formal psychiatric evaluation may allow an improved awareness and documentation.

Pain and analgesic administration have an unclear impact on the ability of a patient to retain decision making capacity. In the setting of laboring women, it is generally agreed by Anesthesiologists and validated by published research that these patients possess decision making capacity [31–34]. Other work has demonstrated that there is no detectable impact of opioid dose on a patient's capacity level or ability to provide consent [35]. However, following an anesthetic, patients are recovering not just from the effects of opioids but also inhaled/intravenous anesthetics and benzodiazepines and in these patients decision making capacity may be significantly unclear.

30.7 Surrogate Decision Makers

If a physician is unable to determine medical decision-making capacity, or if the patient fails the assessment, the next step is to turn to assisted decision making and surrogate decision makers. These methods serve to attempt to best determine what the person wants or would have wanted.

Assisted decision making can be thought of as filling in the gaps. For example, a patient is in severe pain and requesting an intervention but feels as though they cannot process all of the information accurately, they may request assistance from a family member in making a decision. The role of the surrogate assisted decision maker is to preserve of autonomy to the extent possible and identify the areas of spared cognitive function. This allows the surrogate t***o assist*** with areas of impaired cognitive function in order to make a decision.

If the patient is determined to lack decision making capacity by a physician, the next step is a surrogate decision maker. The surrogate must make every effort to make a decision based on what the subject would have decided if capable of consenting, or what is in the best interest of the subject. Generally, two types of surrogate consent laws are recognized: hierarchy surrogate consent laws and consensus surrogate consent laws [36]. Out of the 50 states, 35 are considered hierarchy states where the following persons are designated to serve as surrogates, in descending order: the spouse (unless divorced or legally separated); an adult child; a parent; and an adult sibling. There is substantial divergence after the fourth rung and in the classes and number of classes listed [36]. Some also include class designations for other adult relatives including: grandchildren. In contrast, states that uphold a consensus surrogate decision making standard require that all reasonably available "interested persons" come to a consensus about who should act as the decision-maker. Finally, there is always the option to obtain a formal ethics consult or call the legal department for assistance. This may result in a court appointed guardian and is often not a feasible solution given the timeliness of the situation. It is important for providers to know state statutes and institutional policies when using surrogate decision makers.

30.8 Advance Directives

An advance directive is a legal document that records treatment preferences or designates a durable power of attorney for health care, or both [36]. Unfortunately, the rate of completion of advance directives in the general U.S. population hovers around 20–29% [37, 38]. An advance directive can be in the form of a living will or health care power of attorney. A living will acts as a declaration to physicians and allows the patient to select the kind of life-sustaining care he or she would want in the setting of injury or illness and are not able to make decisions whereas with a health care power of attorney, the patient would appoint a person to act as their "agent" capable of making all health care decisions on their behalf. Often, the document itself will address the requirements in order to activate the healthcare power of attorney. Many require the signatures of two physicians confirming the patient's incapacity.

A specific example of a type of advance directive that might be encountered by anesthesia providers is a pregnant woman presenting with a "birth plan." These directives may provide specific acknowledgements of what analgesic procedures

will and will not be tolerated. For example, these plans may specifically prohibit the administration of neuraxial anesthesia or even delivery by Caesarean section. An additional example of peri-procedural "plans" that may provide challenges to Anesthesia providers might be the patient who, following a preoperative discussion of risks and benefits, refuses regional anesthesia prior to their surgical procedure. Where both of these types of patients create ethical or legal dilemmas is when, in the setting of pain, opioids, duress, sedation, residual anesthesia, etc., these patients now reverse course and request the procedures they previously either forbade or declined. Anesthesia providers may feel that they are forced to choose between withholding analgesia or violating the wishes that were made by a patient when they were of "sound mind."

30.9 Contemporary Considerations

Contemporary Regional Anesthesia and Pain Medicine has presented providers with a variety of additional ethical considerations. For example, providers should consider disclosing to patients the involvement of trainees in the process of analgesic services. It may even be appropriate to disclose the training level and experience of these learners and provide patients with an opportunity to question their level of experience and expected procedural involvement. For novel techniques or equipment, it may be appropriate to disclose provider experience with the proposed intervention, especially if it is significantly limited.

For novel analgesic techniques, it may also be appropriate to disclose the current state of evidence to support these procedures. For example, with novel fascial plane blocks it may be appropriate to describe how there may not be a significant amount of published evidence to support the use of these procedures. The discussion could also describe how there is a strong anatomical foundation to support the implementation of a planned novel fascial plane block and that the expected risk burden is low. In the author's experience, including patients in the decision to undergo novel procedures generally has produced enthusiastic and participatory "co-investigators." In addition to acknowledging unknown potential benefits associated with novel regional anesthesia techniques, it may also be important to disclose potential unknown risks.

30.10 A Blueprint to Approaching Challenging Consent Scenarios

It is important to acknowledge that there is no one approach that will allow practitioners to successfully navigate all potential consent-related quandaries. However, there are a number of concepts that may help to minimize stress and facilitate a favorable patient interaction.

1. Attempt to understand state, local and institutional standards and policies. It is important to recall that standards and policies can change over time. Therefore, intermittent reviews should be taken to ensure adherence and collaboration with institutional legal support may help to improve clarity and eliminate uncertainty.
2. Be cognizant of what resources are available from your local institution or national organizations. The average practitioner may encounter difficulties maintaining their understanding of relevant standards and policies. For that reason, collaboration with institutional legal and ethics colleagues can assist with information acquisition. In addition, various national organizations such as the American Society of Anesthesiologists (ASA) or American Society of Regional Anesthesiologists (ASRA) have published guidelines, patient information and consent material to standardize and improve the consent process. For example, the ASA has published decision aids for patients that may be candidates for epidural and spinal anesthesia. These decisions aids are well written at an appropriate reading level for most patients. They outline relevant risks and provide appropriate risk estimation for patients in a fashion that allows them to understand what the relative risk is for them (i.e. is provides the risk of death from lightning as context for the risk of adverse outcomes following neuraxial anesthesia). If given to patients well in advance of their planned surgical procedure, this document also provides patients with an opportunity to review the information and formulate questions for their Anesthesiologist to help guide them toward a decision.
3. Attempt to establish rapport with the patient and their family/guardians. In the process of establishing rapport, the Anesthesiologist has an opportunity to demonstrate their compassion and dedication to the family and patient. While establishing rapport, it is likely that there will be an increased understanding of the patient's values and background that may impact their decision-making process. In addition, should an unintended adverse outcome occur, there may be a decreased chance of litigation if there has been effort expended attempting to establish rapport.
4. Make an effort to assess competency while obtaining consent. While there are a variety of tests available to specifically assess patient capacity, there is not yet a tremendous amount of data suggesting that these assays are significantly more accurate than the impressions of a trained provider. In unclear cases, consider augmenting your general impression with a capacity assessment aid or utilization of the "teach back" method. If decision making capacity remains unclear, psychiatric colleagues may be able to provide additional guidance.
5. Recall required components of adequate informed consent. Patients need to know that they are the ultimate authority when making the decision presented to them. They need to know what the available treatment options are and that they will be supported if they elect to forego a proposed medical intervention. Patients need to understand the risks associated with proposed interventional procedures and the risks associated with no treatment. In general, it is likely appropriate to

error on the side of too much rather than too little risk disclosure as patients generally seem to prefer to have a reasonably complete understanding of potential risks.

6. Practice preventive ethics. Make an effort to consider how the surgical plan might be altered from what is listed on the surgical consent form. If the surgical procedure changes from a laparoscopic to an open procedure, obtaining consent in the preoperative setting for fascial plane or neuraxial analgesia eliminates many of the consent related ambiguities that might be encountered when attempting to obtain consent in the postsurgical setting. If patients refuse regional anesthesia procedures in the preoperative setting, attempt to reach some understanding in the preoperative setting that outlines how postoperative requests for regional anesthesia services will be managed. In most cases, patients will be comfortable proceeding with the understanding that they are still capable of making the ultimate decision regarding their analgesic care.
7. Document, Document, Document. From a legal perspective, if a conversation or assessment is not documented, it did not occur. There is a lack of consensus and general variability in documentation of consent for anesthesia procedures. In some institutions, consent for anesthesia is contained within the surgical consent and documentation of verbal consent for anesthesia services is either implied or documented elsewhere. At others, anesthesia specific and even procedure specific consent forms exist. If patients possess a specific medical condition that might impact the risk profile of a proposed procedure (i.e. diabetic neuropathy or multiple sclerosis), any additional or condition-specific risk discussions should be documented.
8. Be honest. Acknowledge uncertainties with regard to risk or efficacy of proposed procedures. For novel procedures or novice providers, it may be appropriate to disclose the experience level of the providers with the proposed intervention.

30.11 Summary

- Informed consent is the cornerstone of the physician-patient relationship and serves both a legal and ethical purpose.
- It is a process that requires a significant investment of time and fosters shared decision making between the physician and patient.
- Medical decision-making capacity of a patient is an assessment that should be made by any physician actively providing care and seeking to obtain informed consent.
- Inadequate consent has been shown to have legal implications and therefore it is crucial that providers are aware of and familiar with the legal environment as well as the institutional policies in which they work.

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Chapter 31
Patient with Polypharmacy

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31.1 Introduction

Patients admitted to the hospital who are taking multiple medications pose some of the greatest safety challenges. As the population ages and becomes more medically complex, more medications are used. Complex patients with multiple comorbidities are at increased risk, as more medications are likely to be prescribed for them. Multiple comorbidity is defined as the presence in an individual of two or more chronic health disorders. This is strongly related to age and increases with socioeconomic deprivation. Patients with multimorbidities have reduced quality of life and worse health outcomes compared to those with a single disease. These patients also tend to be the main consumers of health care resources [1]. The growing number of medications being used as part of medical advancements leads to an increased risk of potential adverse events. Polypharmacy is defined as the concurrent use of multiple drugs to treat a single condition or the concurrent use of multiple drugs by a single patient for one or more conditions. Polypharmacy can be divided into two distinct groups—appropriate polypharmacy and problematic polypharmacy [2].It may predispose patients to greater risks for drug interactions and adverse effects related to comorbidities. Despite the risks of polypharmacy, there may be benefits. Using more than one analgesic with different mechanisms of action (called multimodal analgesia) may allow lower doses of each, potentially reducing adverse effects and improving efficacy. It is up to the consulting clinical team to determine if polypharmacy will be helpful or harmful.

The U.S. Centers for Disease Control reports that 82% of American adults take at least one medication, and 29% take 5 or more. Adverse drug effects cause

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approximately 1.3 million emergency department visits and 350,000 hospitalizations each year [3].Several international studies have shown similar results, with an increase in prescribing rates over time, and an increasing number of patients taking 10 or more medications. Analgesics are one of the most commonly prescribed groups of medications, and over-the-counter products are used widely. It is estimated that 17–23% of the population use an OTC analgesic each week [4]. Complementary and alternative therapies are also increasing, with an estimated 38% of the US adult population utilizing these [5].

This chapter will review the possible problematic polypharmacy, providing insight into drug-drug interactions (both pharmacokinetic and pharmacodynamic) as well as drug-disease interactions. It will also review the advantages of appropriate, or rational, polypharmacy. These concepts will be incorporated into the evaluation and management of the patient with polypharmacy and help the consultant determine how and when to de-prescribe.

Patient scenario: A 68-year-old woman is admitted with a 3-day history of worsening back pain and especially left leg pain, which travels all the way down her leg in a non-dermatomal distribution. The patient has a history of lumbar spine surgery 4 years ago but suffered a fall 3 days ago. She was deemed to be a poor surgical candidate and conservative therapy was recommended. Past medical history includes depression, diabetes mellitus type 2 with renal impairment (Serum creatinine 1.8 ng/dL), GERD, coronary artery disease and congestive heart failure (left ventricular ejection fraction 30%). She reports taking the following medications: omeprazole, sertraline, diazepam, cyclobenzaprine, ibuprofen, metformin, pioglitazone, hydrocodone, furosemide, spironolactone, aspirin, and metoprolol.

31.2 Pathophysiology

31.2.1 Problematic Polypharmacy

The greatest danger with polypharmacy is an increase in adverse drug effects. Using multiple medications, including analgesics, may result in amplified drug effects, including adverse effects, drug- drug and drug-supplement interactions, and drug-disease state interactions. The patient consequences include reduced quality of life, an increased risk of falls, emergency room visits and hospital admissions. For the hospitalized patient, this may cause an extended length of stay. The cost to the patient and healthcare system is estimated to be more than $50 billion annually. The estimated annual cost of medication-related morbidity and mortality from non-optimized therapy was $528.4 billion in 2016. This is also associated with an estimated 285,689 deaths annually [6].

Pharmacokinetic interactions. Drug-drug interactions occur when two or more drugs interact in a way that the effectiveness and/or toxicity of one or all drugs are

changed. These may be pharmacokinetic (and pharmacogenetic) or pharmacodynamic in nature. Pharmacokinetic interactions occur when one medication interferes in the absorption, distribution, metabolism and/or excretion of another medication. Most medications, including analgesics, are metabolized in the liver via the cytochrome P450 (CYP) enzyme families. There are more than 100 drugs that inhibit or induce the CYP enzymes, most significantly the CYP2D6, CYP2C19, CYP2B6 and CYP3A4 enzymes, which make up the bulk of Phase I metabolism in the gut and liver. See Table 31.1 for a list of medications that can affect analgesics. There is also new data emerging on variance of the UGT

Table 31.1 Drug interactions with analgesics

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Substrates				
Amitriptyline Duloxetine Methadone Naproxen R-warfarin Theophylline Tizanidine	Amitriptyline Celecoxib Diclofenac Fluoxetine Ibuprofen Naproxen Phenytoin Piroxicam S-warfarin	Amitriptyline Citalopram Diazepam Indomethacin Topiramate	Amitriptyline Codeine Cyclobenzaprine Desipramine Doxepin Duloxetine Fluoxetine Hydrocodone Methadone Mexiletine Morphine Oxycodone Paroxetine Sertraline Tramadol Venlafaxine	Alprazolam Amitriptyline Bupivacaine Buprenorphine Buspirone Carbamazepine Clonazepam Codeine Cyclobenzaprine Diazepam Erythromycin Fentanyl Lidocaine Methadone Prednisone R-warfarin Sertraline Temazepam Tramadol Zaleplon Zolpidem
Inducers				
Carbamazepine Phenytoin	Carbamazepine Cimetidine Fluconazole Fluoxetine Metronidazole	Carbamazepine Phenytoin	Carbamazepine Phenytoin	Carbamazepine Oxcarbazepine Phenytoin
Inhibitors				
Cimetidine Ciprofloxacin	Carbamazepine Paroxetine Phenytoin Sertraline Valproic acid	Fluoxetine Indomethacin Paroxetine Topiramate	Celecoxib Desipramine Fluoxetine Methadone Paroxetine Sertraline Valproic acid	Fluoxetine Sertraline Ketoconazole Cyclosporine

enzymes, which are part of Phase II metabolism, outside of the hepatocellular CYP system. Pharmacogenetic variances in enzyme activity affect some analgesics and this testing is being more frequent. The analgesics most significantly affected by pharmacogenetic variance utilize the CYP2D6 pathway, such as codeine, tramadol and duloxetine.

Pharmacodynamic interactions occur when one medication counteracts or amplifies the clinical effects of another. A well-known counter effect with analgesics would be an increase in blood pressure seen with NSAIDs added to baseline antihypertensives or the constipating effects of concurrent opioid and tricyclic antidepressant use. The classic additive effect with analgesics is concurrent use of opioids and other CNS depressants, such as benzodiazepines, causing amplified sedation and respiratory depression.

Drug-disease state interactions occur when medications have either positive or negative effects on a disease state. (See Table 31.2) The very young are at risk due to organ systems that are not fully developed (like the CYP enzymes). Pediatric patients with cancer-related or serious medical illnesses are at risk due to multiple toxic medications being used (e.g. chemotherapy, antibiotics, etc). Elderly patients are also at higher risk due to their inherent age-related decrease in organ system function such as hepatic metabolism and renal clearance. They have a higher risk of gastrointestinal and cardiovascular toxicity with NSAIDs, and they are at risk for falls and delirium with opioids and anticonvulsants. Even in patients who are not at inherently increased risk have comorbidities that can pre-dispose them to analgesic-disease state toxicity. This might include the increased risk of opioid-induced respiratory depression with comorbidities like central or obstructive sleep apnea and respiratory disease. Surgical patients are at risk due to post-operative dehydration and fluid shifts, electrolyte imbalances, blood loss, and blunting of bladder and bowel function.

Table 31.2 Pharmacodynamic interactions with analgesics

Analgesic	Avoid/use with caution in
Acetaminophen	Liver disease, concurrent alcohol use (>2 drinks/day)
NSAIDs	Kidney disease, cardio/cerebrovascular disease, PUD, bleeding disorder (except COX-2 selective agents)
Opioids	Respiratory disease, poor gut motility, urinary retention, cognitive impairment, caution with liver disease (fentanyl, methadone, oxycodone, hydrocodone, tramadol, codeine, buprenorphine) and kidney disease (morphine, hydromorphone)
Local anesthetics	Cardiac disease, liver disease
Anticonvulsants	Kidney disease, heart failure and fluid overload (gabapentinoids), liver disease, hyponatremia and bone marrow suppression (carbamazepine, oxcarbazepine), kidney stones, acidosis and narrow angle glaucoma (topiramate)
Antidepressants (SNRIs)	Genitourinary disease, poor gut motility, cognitive impairment, and narrow angle glaucoma (TCAs), cardiac conduction problems (TCAs, milnacipran, higher dose venlafaxine), liver disease (duloxetine)
Muscle relaxants	Liver disease, cognitive impairment

31.2.2 Appropriate or Rational Polypharmacy

Polypharmacy methods have long been utilized in a positive way. Appropriate polypharmacy may reduce adverse effects and intolerances of each of the agents, allowing lower doses to be used (e.g. opioid-sparing effect). Using a combination of agents (e.g. long-acting and short-acting opioids) may allow more effective titration of benefit and more individualization. It also allows a more broad-spectrum approach to management by targeting different causes of pain like the neuropathic and inflammatory processes seen in the surgical setting. Patients with chronic pain that have multiple comorbidities may benefit from multimodal therapies (e.g. patient with depression and neuropathic pain may get dual benefit by adding an SNRI to an anticonvulsant). While not ideal, additional medication may be necessary to avoid adverse effects of a primary analgesic (e.g. laxative regimen with opioids).

Multimodal analgesia in acute pain Early recovery after surgery (ERAS) protocols are being implemented with the intention of reducing opioid-related adverse effects and enhancing recovery [7]. The pharmacological component of these protocols may include acetaminophen, NSAIDs, muscle relaxants, gabapentinoids and opioids, or some combination of these. These protocols also employ neuraxial analgesia techniques or peripheral nerve blocks. This multimodal approach is also called "balanced analgesia" or "rational polypharmacy". The goal is to improve analgesia and reduce dose-related adverse effects by giving lower doses of analgesics with different mechanisms of action. However, these combinations must be individualized to each patient.

Multimodal analgesia in chronic pain is utilized commonly. This technique has been utilized in several different chronic disease states such as cardiovascular disease, using aspirin, a beta-blocker, a statin and an ACE inhibitor to reduce risk. Patients with multiple comorbidities in the pain setting may need more than one analgesic. For example, a patient with acute on chronic back pain. These patients may have a radicular component to their pain, an arthritic component (as with facet arthropathy) and/or muscle spasms or myofascial pain. Since there isn't one analgesic that can manage each of these characteristics, clinicians may end up with a combination of analgesics. Patients may also have more than one type of pain such as diabetic peripheral neuropathic pain and osteoarthritis. In this case the neuropathic and musculoskeletal pain will likely be treated with different agents. Again, these regimens must be individualized to each patient.

31.3 Risk Factors

Risk factors for adverse outcomes related to polypharmacy include patient factors, medication factors, provider factors and system factors [2, 8–10].See Table 31.3 for further information. It is well-known that the number of medications a patient takes is related to the risk of adverse consequences. The number grows with

Table 31.3 Risk factors for polypharmacy

Patient factors	Drug factors	Provider factors	System factors
Older age	Mechanism of action	Lack of education/ competency	Disjointed electronic medical records
Female gender	Pharmacokinetics	Personal beliefs/biases	Poor inter-provider communication
Ethnicity and cultural beliefs	Pharmacodynamics	Prescribing practices—off-label use, aggressive treatment utilizing multiple therapies	Ineffective transitions of care
Lower socioeconomic status	Efficacy	Over-referral, multiple specialties	Increased number of products available (prescription, OTC, CAM)
Number of co-morbidities which affect cognitive and physical function	Formulations	Poor provider-patient communication	Inconsistent/non-evidence-based insurance enforcement guidelines
Patient ability to accurately self-report use of medications, OTC products and CAM therapies	Adverse effects	High workload, limited time	Multiple disease-specific guidelines in patients with several chronic disease states
Non-compliance	Cost	Lack of guidelines/ standardization	Direct to patient marketing
Increasing use of OTC and CAM therapies			
Use of multiple providers and pharmacies			
Higher number of medications			

increasing age and with greater chronic disease states [10].However, age is not the strongest co-predictor of adverse effects with polypharmacy. It is related more to the number of comorbidities a patient has than to the patient's age [11]. Polypharmacy also sets up risks for medication administration including phonetic confusion, dosing errors and pill visual-cue errors. System weaknesses need to be identified. Risk factors for inappropriate prescribing that are associated with systems of care include: discharge from hospital/facility in last 4 weeks, multiple doctors/health professionals, need for caregivers after discharge, and recent medication changes. These risk factors highlight the significance of interfaces between the hospital and primary care, home or residential care, and between health professionals [2]. These transitions of care points are where care can become fragmented, and where good communication and documentation are most needed, but often lacking.

31.4 Identification and Evaluation

There is much advice on when to initiate a medicine, but there is far less information and evidence to help support decisions to stop therapy. Several different sets of criteria have been validated for identifying potentially inappropriate medications (PIM) in elderly patients. The original was the Beer's criteria, which has been updated several times. Two sets of criteria have been developed in Ireland and are extensively used in the UK to assess whether medicines have been inappropriately prescribed or omitted: The Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START). STOPP comprises 65 clinically significant criteria for potentially inappropriate prescribing in older people. Each criterion is accompanied by a concise explanation as to why the prescribing practice is potentially inappropriate. START consists of 22 evidence-based prescribing indicators for commonly encountered diseases in older people [12]. Utilization of these tools have significantly reduced adverse drug effects (absolute risk reduction of 9.3%) when applied within 72 h of hospital admission and reduced average length of stay by 3 days in older people with acute illness [13].

- All patients should have a complete medication history, including OTC, CAM and dietary supplements. This evaluation may include consulting with the patient's pharmacy or local provider and any prescription databases, to verify drug, dose and refill history. Then, each medication should be matched with a disease state or clinical indication. The patient should be assessed for pre-existing comorbidities or new-onset changes in organ function, particularly if these can be predicted (e.g. compromised renal function after cystectomy or ileus after bowel resection).
- Consider utilizing screening tools such as the STOPP/START to identify potentially inappropriate medications for people ≥65 years of age. (See Tables 31.4, 31.5, and 31.6).

Table 31.4 STOPP criteria for CNS medications

1. Tricyclic antidepressants (TCA's) with dementia
2. TCA's with glaucoma
3. TCA's with cardiac conductive abnormalities
4. TCA's with constipation
5. TCA's with an opioid or calcium channel blocker
6. TCA's with prostatism or prior history of urinary retention
7. Long-term (>1 month), long-acting benzodiazepines/benzodiazepines with long-acting metabolites
8. Long-term (>1 month) neuroleptics with long-term hypnotics
9. Long-term neuroleptics (>1 month) in those with parkinsonism
10. Phenothiazines in patients with epilepsy
11. Anticholinergics to treat extra-pyramidal side-effects of neuroleptic medications
12. Selective serotonin re-uptake inhibitors (SSRI's) with a history of clinically significant hyponatremia
13. Prolonged use (>1 week) of first generation antihistamines

Table 31.5 STOPP criteria for musculoskeletal medications

1. NSAID with history of PUD or GI bleeding, unless concurrent H2 blocker, PPI or misoprostol
2. NSAID with moderate-severe HTN
3. NSAID with heart failure
4. Long-term use of NSAID (>3 months) for symptom relief of mild osteoarthritis
5. Warfarin and NSAID together
6. NSAID with chronic renal failure
7. Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis or osteoarthritis
8. Long-term NSAID or colchicine treatment of gout where there is no contraindication to allopurinol

Table 31.6 STOPP criteria for analgesic medications

1. Use of long-term powerful opioids (e.g. morphine or fentanyl) as first line therapy for mild-moderate pain
2. Regular opioids for more than 2 weeks in those with chronic constipation without concurrent use of laxatives
3. Long-term opioids in those with dementia unless indicated for palliative care or management of moderate-severe chronic pain

Table 31.7 Mediation Appropriateness Index (MAI)

1. Indication: the sign, symptom, disease or condition for which the medication is prescribed
2. Effectiveness: is it producing a beneficial result?
3. Dosage: total amount of medication taken per 24-h period.
4. Directions: instructions to the patient/staff for the proper use of a medication
5. Practicality: capability of being used or being put into practice
6. Potential for drug–drug interaction(s)
7. Potential for drug–disease interaction(s)
8. Unnecessary duplication: non-beneficial or risky prescribing of two or more drugs from the same chemical or pharmacological class
9. Duration: length of therapy
10. Expensiveness: cost of drug in comparison to other agents of equal efficacy and safety

- Currently we do not have a reliable and validated risk prediction model, though several have been evaluated [14]. Consultants should consider reviewing medications in all patients with 10 or more regular medicines (particularly high-risk medications like opioids and NSAIDs) or patients receiving 4–9 regular medicines who also have at least one other risk factor (see Table 31.3) and those who have experienced previous adverse drug effects.
- Consider utilizing assessment tools such as the Medication Appropriateness Index (MAI) [2] (See Table 31.7).

- Signs and symptoms of toxicity should be evaluated including vital signs and labs, cognitive function and organ function (urine output, etc.), as well as a general and specific assessment of the pain complaint.
- Investigations—Consultants should determine if clinical guidelines are being followed, if there are medications that do not have an indication, or if there are indications that are not being managed appropriately. With regard to pain management, are appropriate multimodal regimens being implemented? Have adjustments been made for the individual patient?
- Consider de-prescribing—De-prescribing is the process by which medications are reviewed and stopped if not clinically beneficial. Patients with uncontrolled pain may have different analgesics added to his/her regimen without assessment of the effectiveness, Table 31.8. See Table 31.9 for a list of questions.

Table 31.8 Patient case scenario—evaluation

Indication	Medication	Potential problems
Back pain	Cyclobenzaprine Ibuprofen Hydrocodone Diazepam	Ibuprofen is contraindicated in CHF, CAD, renal impairment, ±GERD Diazepam is relatively contraindicated with patients >65 years of age Two muscle relaxants (diazepam, cyclobenzaprine)
GERD	Omeprazole	NSAID in the setting of GERD
Diabetes mellitus Type 2	Metformin Pioglitazone	Pioglitazone with ibuprofen in a patient with CHF, see below
Renal impairment		NSAID in the setting of renal impairment
Coronary artery disease	Aspirin Metoprolol	NSAID in the setting of CAD. NSAID May compromise the effectiveness of ASA.
Congestive heart failure (EF 30%)	Furosemide Spironolactone	Pioglitazone causes fluid retention and will exacerbate any fluid retention caused by NSAID. May be treating the side effect of a medication (pioglitazone, ibuprofen) with another medication (spironolactone, furosemide)
Depression	Sertraline	An SSRI and a diuretic may cause additive hyponatremia risk

Table 31.9 De-prescribing questions

1. Is the drug still needed?
2. Has the condition changed?
3. Can the patient continue to benefit?
4. Has the evidence changed?
5. Have the treatment guidelines changed?
6. Is the drug being used to treat an iatrogenic problem?
7. What are the ethical issues about withholding care?
8. Would discontinuation cause problems?

31.5 Pain Assessment Tools

The usual pain assessment tools may be used, ideally multidimensional tools that address comfort and function. Clinicians also need to educate patients, families and bedside caregivers of the signs and symptoms of toxicity and implement any additional safety monitoring.

31.6 Management of Pain in the Inpatient Setting

The first step is to determine if the current analgesics are necessary or if simplification can be made safely and effectively. Multifactorial pain, such as with surgery or low back pain, often calls for more than one pharmacologic approach. This should be driven by the strongest evidence available. However, if there is an immediate or significant safety risk, the ideal regimen may need to be modified.

Non-pharmacological management is always first-line therapy for both acute and chronic pain. This would avoid adding medications to complex regimens. Options include everything from heat and ice to aromatherapy, music therapy or relaxation/meditation techniques.

Interventional techniques mostly avoid systemic circulation and interactions, so would be ideal if the situation is amenable. Regional or neuraxial techniques for surgical patients are an excellent choice if possible.

A complete history and physical as well as medication history should be undertaken before a plan is implemented. For example, if a patient with coronary artery disease presents pre-operatively for a total hip arthroplasty, the usual COX-2 selective NSAID should be avoided, due to the increased risk of coronary or cerebral vascular events. Some parts of the regimen may simply need to be modified, such as a gabapentin dose reduction in a patient with renal compromise. This is all workable if a consist process is implemented.

Clinical options in the face of drug interactions include stopping one or more of the interacting medications, switching one or more of the medications, or adjusting the doses of one or more of the medications. The option chosen will depend on how critical the clinical situation is, and what alternatives are available.

Patient scenario: Our patient example shows a common scenario seen in an acute care setting. Acute low back and leg pain is a relatively common condition seen in emergency rooms in the US [15]. *In this patient scenario we have a patient with polypharmacy that may make therapeutic options difficult. This particular patient is currently taking opioids, benzodiazepines, as well as a muscle relaxant. If the current therapy is not providing adequate analgesia it would be difficult to justify increasing these medications with the classic additive effect of opioids and other CNS depressant causing additive risks of sedation and respiratory depression. Eliminating the CNS depressant(s) may allow for a higher dose of her analgesic, hydrocodone, without increasing the risk for respiratory depression.*

31.7 Discharge Plan for Pain Management

Discharge planning should include a medication reconciliation process to ensure that when patients are discharged, their plan and any changes made during their hospitalization are communicated effectively and efficiently to the patient's primary outpatient team. It has been shown that this process can reduce ADE-related visits to the ED and readmissions [16].

The discharge process should include a discussion with the patient and caregivers about management of pain after discharge. This includes ensuring that medication changes, additions and discontinuation of any home medications are reviewed to avoid confusion. Education and counselling about new medications is imperative. There needs to be adequate coordination between the hospital, community health services, local pharmacies, primary care practices and any pain specialists that the patient may receive care from. Follow-up (phone or clinic visit) reduces the risk of readmission. It is ideal to have the patient involved in the decision-making process, called shared decision making. This can be especially helpful when deprescribing, as the patient may report that a particular medication is actually not effective or does cause some side effect.

31.8 Summary

See Table 31.10.

Table 31.10 Conducting a polypharmacy evaluation

Conduct a physical exam and history, identify type of pain that the patient has (neuropathic, musculoskeletal, etc.)
Conduct a thorough review of other chronic disease states
Review the evidence available regarding the treatment of the type of pain the patient has (non-pharm, interventional, pharmacologic, etc.)
Conduct a thorough review of all the patient's past and present treatments and medications (including OTC and CAM products)
Determine, with the patient, which treatments/analgesics have been helpful and which may have been ineffective or caused adverse effects
If any of the patient's current analgesics pose a risk, have been ineffective or caused adverse effects, these should be stopped or tapered
Make a list of all possible and reasonable options, taking into account co-morbidities and possible drug interactions
Review these with the patient, to determine if there are any concerns. Educate the patient on adverse effects and expected efficacy. Some therapies will take several weeks to titrate to a therapeutic dose (such as anticonvulsants) and the patient should be counseled about this
Efficacy and adverse effects should be reviewed on a daily basis while in the hospital, adjusting dose and regimen as needed
Discharge planning should include communications with the patient's local team (provider, pharmacy, etc.). The patient should be given written and verbal instructions with regard to how to take the analgesic regimen

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Chapter 32
Patient with Sepsis

Arjun Ramesh and Samuel W. Samuel

32.1 Introduction

The management of pain in intensive care unit (ICU) patients can be very challenging. This is exacerbated in the septic patient, where a mean arterial pressure greater than 65 is a goal of therapy in order to maintain end organ perfusion [1]. These patients will often require aggressive resuscitation and vasopressor support. Due to the nature of the disease, they often have end organ dysfunction which further complicates their care. This is particularly important when it affects the liver or kidneys as this can allow for the buildup of active or toxic metabolites of medications. As such, the choice of modality for pain control can often be difficult and limited. Many commonly used medications such as narcotics, muscle relaxants, alpha 2 agonists, and nonsteroidal anti-inflammatory drugs, as well as neuraxial techniques, although common, can cause dangerous drop in blood pressure when used for pain control in the septic patient. In addition, removal or obliteration of the resultant sympathetic response to pain can also cause a drop-in blood pressure which may not be well tolerated. Thus, commonly used modalities are less feasible in these patients, and increased care must be taken when recommending a pain control regimen. In general, the adage of "start low and go slow" should be followed, and side effects should be minimized where possible.

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32.2 Pathophysiology

Sepsis is defined as "a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection" [1]. It was previously identified by considering the "SIRS" criteria, which required two of the following four criteria: temperature >38 °C or <36 °C, heart rate >90/min, respiratory rate >20/min or $PaCO_2$ < 32, and white count >12,000 or <4000 or >10% immature bands. However, this definition does not account for all of the elements of sepsis as it focuses on inflammatory excess. Other factors, such as cardiovascular, neuronal, autonomic, hormonal, bioenergetic, metabolic, and coagulation changes are not encompassed by that definition. These include decreases in blood pressure mediated by cardiac, inflammatory, and autonomic mechanisms, increases in stress hormone secretion, decreased energy availability due to both decreased energy stores and inadequate perfusion of tissue, acidosis which accompanies those changes, and systemic activation of the coagulation cascade. All of these contribute to the organ dysfunction and hemodynamic instability that is commonly seen in these patients.

A precise definition of sepsis is further complicated as the exact pathophysiologic drivers for many of these changes are unknown. The sequential (sepsis-related) organ failure assessment score (SOFA) and quick SOFA (q-SOFA) scores are now being used to replace the SIRS criteria as they provide a better global assessment of organ dysfunction compared to the SIRS criteria [1]. In regard to pain management, the hemodynamic instability and metabolic dysfunction seen in these patients is the largest challenge when choosing an appropriate treatment, be it medication or intervention. Ultimately sepsis is the result of a complex interplay of a variety of biologic systems in response to an infectious insult.

32.3 Risk Factors

Septic patients can have many reasons for pain. It could be due to their primary injury, or could be due to pathophysiologic changes in the septic patient such as an increase in proinflammatory mediators as these can cause an increase in pain unto themselves [2]. Pain is readily recognized in patients who have obvious injuries, such as surgical incisions, burns, kidney stones, etc. However, due to the pathophysiologic changes in the septic patient, pain can present later in the course of the disease and regular pain assessments should be utilized. In addition, severe sepsis and increasing age are risk factors for the development of chronic pain after ICU discharge [3].

32.4 Diagnosis

The diagnosis of pain in the septic patient can be difficult. If these patients are sedated and intubated, they may be unable to communicate pain scores. Additionally, the usual physiologic indicators of pain such as hypertension and tachycardia may

be ablated given the disease. In septic patients with obvious injuries (such as surgical incisions or burns) pain should be suspected even if the patient is unable to communicate the degree of pain. The behavioral pain scale and critical care pain observation tool can provide clues to the presence of pain in patients who are otherwise unable to communicate [4, 5]. However, the cause of the pain may not always be obvious as occult lesions or changes in inflammatory mediators may be the cause. Imaging studies and clinical exam are beneficial in helping to narrow the differential diagnosis for the cause of pain.

32.5 Treatment

The treatment of pain in the septic patient can be challenging as there are numerous goals of care which may run counter to each other. Maintaining hemodynamics is paramount in these patients, but the painful stimulus may be assisting in this goal. In addition, organ dysfunction can complicate the choice of intervention. Pharmacologic and interventional management should be utilized in a manner that complements the treatment goals and minimizes unwanted side effects.

32.5.1 Pharmacological Management

While medications are a commonly utilized intervention for the treatment of pain in the inpatient setting, there is little data to guide care in the septic patient. Avoidance of hypotension, as discussed above, is imperative in these critically ill patients. In these patients, pain can be a major driver of sympathetic tone, and obliteration of such a stimulus can lead to a drop in blood pressure with a resultant decrease in end organ perfusion. This can lead to worsening of the disease process and in some cases death. Thus, it is paramount to be judicious in the use of analgesic medications. In addition, consideration of metabolism is prudent, as many patients will have some degree of end organ dysfunction, requiring dose adjustment or precluding the use of certain agents. Drugs which are metabolized in an organ independent manner, and those with no active metabolites should be preferred. Short acting medications are also preferred to long acting medications as they can be quickly stopped if adverse reactions are seen. We will discuss the commonly used pain medications and their potential hazards in this patient population below.

32.5.2 Narcotics

Narcotic pain medications are a mainstay of inpatient acute pain management. These medications cause significant pain relief in the short term. In addition, patient controlled analgesia (PCA) is an excellent delivery method, with increased patient

satisfaction scores and decreased burden on ancillary staff. However, care should be used in septic patients when prescribing these medications. If a narcotic is to be used, a short acting agent should be used initially, as they can cause a dangerous decrease in blood pressure. There is also data that shows an increased mortality in patients who are on narcotic medications prior to hospitalization for sepsis [6]. Alterations in mental status from drug effect can confuse the picture in a patient who is declining clinically from their underlying pathology. There is also evidence that morphine use can suppress both the innate and adaptive immune response [7]. In a septic patient downregulating the immune system would be counter to the goals of therapy and as such should be avoided if possible. While narcotic medications are not contraindicated in the septic patient, they should be used judiciously. Fentanyl would be an excellent choice as it has a relatively short duration of action, no active metabolites, and potent analgesic effects.

As these medications are relatively cardiac stable, they can be used in the setting of reduced ejection fraction sometimes seen in ICU patients. As discussed above end organ damage, particularly to the liver and kidneys should be considered when starting narcotics such as morphine, which have active metabolites. PCAs can be used as they allow for decreased work for nursing staff while increasing patient satisfaction.

32.5.3 Muscle Relaxants

Many advocate for the use of muscle relaxants as part of a multimodal pain control regimen [8]. However, these medications should be considered individually due to their varied mechanism of action. Tizanidine and Carisoprodol can cause hypotension via a mechanism independent of their pain-relieving qualities [9]. However, even medications which are not generally associated with hypotension should be used with caution, as the analgesic effects and polypharmacy which is common in septic patients can result in inadvertent hypotension, further altering mental status or other adverse effects specific to each muscle relaxant. Thus, the clinical picture will dictate the best muscle relaxant to use in the given circumstance.

32.5.4 Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

While there are no clear studies to point towards or against the use of NSAIDs in septic patients, it would seem that these medications could be used relatively safely. In fact, there are currently trials underway to investigate the relationship between early aspirin therapy and a decrease in mortality in septic patients [10]. While there is a relationship between prehospitalization aspirin use and mortality, there is currently a lack of evidence to guide its use in the septic patient after hospitalization. In

either case the use of NSAID therapy in septic patients is likely a reasonable step in allowing for pain control without increasing the risk of potential adverse effect from therapy. Fluid status, renal function, cardiac status, and bleeding tendency should be carefully assessed prior to initiation of NSAIDs therapy, as the use of this class of medications may cause harm in patients with these disorders.

32.5.5 Other Medications

As there is no clear evidence to guide analgesic therapy in the septic patient, the goals of therapy should be considered when recommending a certain analgesic regimen. The most important goal is to provide analgesia without significant hypotension. To that end, adjuvant medications such as clonidine, which are sometimes used to potentiate the effects of other analgesics should be avoided as they can cause an unacceptable decrease in blood pressure. Ketamine, an N-methyl-D-aspartate antagonist, has been used effectively in septic patients, and initiation at a low dose could be considered as part of a narcotic sparing regimen [11]. However, as it is a direct acting cardiac depressant, care should be taking with its initiation particularly if the patient already requires vasopressor support. It does offer an indirect sympathetic effect, but in critically ill patients, this effect is often attenuated. Neuropathic pain medications, such as gabapentin and carbamazepine may also be useful in controlling pain in the critically ill patient, although these have not been explicitly studied in the setting of sepsis [11]. Gabapentin specifically may cause an increase in edema and should be used with caution in patients with congestive heart failure. Even relatively benign medications such as acetaminophen should be used judiciously, as liver injury from the medication can be potentiated in the setting of sepsis and could lead to liver failure if used without caution.

Acetaminophen deserves special mention as it is a relatively safe and potent analgesic agent. In addition, it is helpful in the treatment of fevers often seen in septic patients. It has even been suggested that the early initiation of acetaminophen in the treatment of sepsis can result in decreased rates of oxidative injury and improved kidney function [12]. In those patients who are unable to take oral medications, there is also an intravenous formulation which has been widely used. This would be particularly attractive in patients who are hypotensive, where the enteral absorption may be compromised [11]. While it has anecdotally been shown to improve pain control compared to the oral route, this has not been born out in large studies [13]. It may also cause hypotension in up to 50% of patients [11]. Additionally, early initiation of acetaminophen by the intravenous route has not been shown to decrease the length of intensive care unit stay versus placebo, although this data studied specifically its antipyretic and not its analgesic effects [14]. Ultimately the choice of whether or not to initiate acetaminophen therapy and the route of administration will be dictated by the specific clinical scenario.

32.5.6 Interventions

While interventional therapies may be attractive in the septic patient as they avoid the risks associated with medications, they are not without their own risks. As neuraxial and regional techniques have somewhat different considerations we will discuss them separately.

32.5.6.1 Neuraxial Techniques

Sepsis is a relative contraindication to the placement of an epidural or spinal catheter. As the patient already likely has an infection, it would be potentially disastrous if the infectious organism was to translocate to the epidural space or to within the thecal sac. In addition, the decrease in blood pressure which accompanies the sympathectomy established by epidural and spinal analgesia may not be well tolerated. These patients may also have the need for unexpected procedures with anticoagulation, which could be complicated if there is an epidural catheter in place. Nonetheless, epidural analgesia may provide some benefit in an appropriate patient population. There is some evidence to show that thoracic epidurals may improve splanchnic flow, and thus decrease the risk of bacterial translocation from the gut to the bloodstream [15]. However, while this benefit may exist, more robust trials are needed to support the routine use of epidural analgesia in the septic patient. If the patient is anticoagulated as part of their therapy, the guidelines established by the American Society of Regional Anesthesia should be consulted regarding appropriate timing for placement of removal of neuraxial blocks.

32.5.6.2 Peripheral Techniques

While the placement of a peripheral single shot block or a peripheral catheter is less risky than placing an epidural or intrathecal catheter in a septic patient, these blocks should still not be performed without careful consideration. As mentioned in the previous section, septic patients may require urgent procedures, and placement of a peripheral catheter could interfere with the ability to anticoagulate a patient should the need arise. While a benefit of a peripheral block is the lack of sympathectomy while still producing analgesia in the target region, there is still the risk of creating a new abscess at the blocksite. This is heightened if the needle entry site is inflamed or shows signs of cellulitis. In general, care should be taken when performing a peripheral block on a septic patient.

While targeted peripheral nerve blocks have been commonly used in the past, newer fascial plane blocks are being more commonly utilized. While there is a theoretical benefit to performing these blocks in a septic patient, as there is less risk of ceding an infection in close proximity to a peripheral nerve, there are very few reports of these procedures being performed in this patient population. These reports include many commonly performed blocks including the transversus abdominis

plane block, quadratus lumborum block, and erector spinae block [16–18]. As these have reportedly been successful elsewhere, fascial plane blocks can be considered in septic patients, with precautions similar to performance of a peripheral nerve block.

32.5.7 Other Modalities

There are numerous non-interventional, non-pharmacological interventions which can be considered for pain management. These have the benefit of causing minimal alteration in hemodynamics, and not relying on the intrinsic function of various organs. Massage, music, and mindfulness are all valid approaches, although their utility may be limited. Additionally, it required staff with training in these modalities which may not be available in all instances. If feasible, these can be included in the pain regimen for these patients [11].

32.6 Pain Assessment Tools

Pain assessment in the critically ill patient continues to be a daily clinical challenge. Patient self-report of pain remains the gold standard for pain assessment and should be evaluated whenever possible. However, when the clinical condition does not allow for such assessment (patient sedated, intubated) then other pain assessment tools should be used.

The two most common assessment scales for patients in the ICU are Behavioral Pain Scale (BPS) and the Critical-care Pain Observation Tool (CPOT).

32.6.1 Critical-Care Pain Observation Tool (CPOT)

The CPOT includes four behavioral categories: facial expression, body movements, muscle tension, and compliance with the ventilator for intubated patients or vocalization for extubated patients. Items in each category are scored from 0 to 2 with the total score of the CPOT ranging from 0 to 8 [4].

32.6.2 Behavioral Pain Scale (BPS)

The BPS, comprised of the original BPS and the BPS-NI (non-intubated), includes three behavioral indicators: facial expression, movement of upper limbs, and compliance with ventilation for intubated patients or vocalization for the non-intubated.

Each indicator is rated from 1 to 4 with a total BPS score possible ranging from 3 to 12 [5].

Family members may help also in the identification of pain related behaviors and should be more involved in pain assessment process. Although vital signs can change with increased pain they should be used as cues for further assessment of pain with the appropriate tools as they could be caused by the underlying clinical pathology rather than pain.

32.7 Challenges in Management of Pain While in the Hospital

As mentioned previously, the management of pain in the septic patient involves balancing the therapeutic goals with the side effects of the therapies used. Careful assessment of the patient's hemodynamic status and organ function is critical in determining the appropriate therapy to use in each situation. A patient with severe liver dysfunction may not tolerate treatment with acetaminophen, while a patient with severe kidney injury may not be a good candidate for NSAIDs. Given the tenuous nature of these patients it is imperative to tailor the therapy to the patient's clinical status. Conservative therapies such as acupuncture, yoga, massage, and mindfulness all have their place, but may be difficult to coordinate in some settings. Specific considerations for each therapy and medication class and intervention is mentioned previously in this chapter.

32.8 Management of Pain in the Inpatient Setting

The management of a septic ICU patient is difficult as mentioned previously. Given the tenuous nature of these patients, treatment plans must be individualized given each situation. As always, a thorough history and physical exam, as well as review of the patient's hospital course will help guide appropriate interventions. Maintaining appropriate vital signs, avoiding medications with potentially dangerous side effects, and planning for possible future interventions or surgeries which may be required for the patient to improve, should all be considered before offering any interventional or pharmacologic treatment. A multimodal approach with the goal of minimizing side effects which providing appropriate analgesia should be employed. Discussion with other managing services to determine the exact goals of treatment will allow for the formulation of the ideal treatment plan in each given scenario.

32.9 Discharge Plan for Pain Management

Patients are rarely discharged directly from the ICU. When they are, adequate follow-up is paramount. Lack of follow up can lead to inappropriate use or misuse of prescribed medications [19]. Ideally, the patient will have the appointment scheduled prior to discharge, and medications at discharge can be written until the patient's scheduled appointment. This is particularly important in the case of narcotic pain medications as this will decrease the risk for misuse and abuse. However, patients are often moved from the ICU to a unit with a lower level of monitoring prior to discharge. If the patients are pain free prior to being discharged, no dedicated pain management follow up may be needed. This will depend on the patient's status at the time of discharge. In general, if the patient is requiring pain medication, close follow up should be initiated with the patient's primary care provider, or with a dedicated pain management clinic, depending on the severity of the patient's pain and medications prescribed at discharge.

32.10 Summary

- Clinical status must be thoroughly assessed as these patients often have a tenuous clinical status.
- Multimodal medication management should be initiated with medications of multiple classes. A narcotic agent, muscle relaxant, neuropathic agent, and NSAID can be initiated if appropriate.
- Medications should be chosen so as to minimize hypotension.
- Medications without active metabolites should be preferred.
- Short acting agents should be preferred until the patient has been shown to tolerate them and is clinically stable.
- Interventions can be considered based on the location of the pain, and feasibility of the intervention (anticoagulation status, planned procedures, ability to place indwelling catheters, etc.).
- Risks and benefits of all interventions should be discussed with the patient and family prior to proceeding with an intervention.
- Conservative therapies should be offered as tolerated by the patient and available at the institution.
- The patient should be closely monitored, and interventions modified based on patient response.

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Chapter 33
Patient with Short Gut Syndrome

Priyanka Singla and Lynn R. Kohan

33.1 Introduction

SBS is a malabsorption condition resulting most commonly from extensive resection of the small intestine. SBS, however, can also occur secondary to disease, injury, or any condition that hinders or impacts the proper function of the small bowel even if the small bowel is entirely intact [1]. Patients with SBS may experience a significant decreased quality of life. Patients with SBS are at risk for developing several complications including complications from the underlying disease, altered bowel anatomy or its function, or its treatment including the need for parenteral nutrition.

The management of SBS is complex usually necessitating a multidisciplinary team approach to optimize care. An integral member of this team should often include the pain management physician. Not only do patients with SBS suffer comorbid pain from the disease itself, but the altered bowel anatomy and function can significantly impact the absorption of medications needed to treat other common pain related disorders.

This chapter will seek to review the pathophysiology of the disease, risks, and signs and symptoms of the disease in order to provide the pain physician with a better understanding of the condition to optimize care of these patients.

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33.2 Pathophysiology

In order to understand how best to treat pain in patients with SBS, it is important to understand the pathophysiology of the disorder. The normal adult human small bowel is approximately 300–600 cm in length and consists of three different segments: the duodenum (25–30 cm), the jejunum (160–200 cm), and the ileum. SBS generally develops when two thirds of the small intestine is resected [2]. The anatomic site and extent of disease or resection determines the patient's risk of developing fluid and electrolyte imbalances as well as nutritional derangements from malabsorption [3]. The absorption of carbohydrates, proteins, and fat as well as micronutrients typically occurs in the duodenum and jejunum, while the ileum typically serves as the main site of bile salt, vitamin B12, and magnesium absorption [4]. The distal ileum is also important for the regulation of gastric emptying and small bowel transit time. Resection/loss of function in this segment can therefore can slow gastric emptying and intestinal transit [4]. In addition, the ileum is responsible for the majority of fluid absorption (approximately 7 L) while the remaining 1–2 L pass into and are absorbed by the colon [5]. Malabsorption is impacted by the presence or absence of an intact colon and whether or not it is contiguous with the small bowel. The ileocecal valve links the small intestine with the colon. Its presence or absence can also affect absorption since it helps to regulate intestinal transit time [6]. The portion of the small bowel that is resected or functionally impacted is therefore important. The ileum is able to adapt structurally if the jejunum is resected, however the jejunum is unable to acquire the site-specific absorption capabilities of the ileum [7].

Understanding the basics of intestinal absorption is important because essentially all oral medications are absorbed in the small intestine, therefore their absorption will be impaired in patients with SBS [8]. Furthermore, medications that rely on enterohepatic circulation are impacted when >100 cm of the ileum is resected or diseased. The degree of medication malabsorption is not predictable and can even vary day to day in the same patient secondary to changes in intestinal transit time that can occur with variations in dietary intake.

Malabsorption can lead to a plethora of complications including malnutrition, weight loss, steatorrhea, diarrhea, dehydration, electrolyte imbalance, and vitamin deficiencies [9]. Additional complications include nephrolithiasis secondary to hyperoxaluria, cholelithiasis, transient gastric hypersecretion, bacterial overgrowth, hyponatremia, potassium deficiency, magnesium deficiency, and D-lactic acidosis. In addition, as mentioned above drug absorption can be profoundly affected by both loss or decreased function of the small bowel leading to difficulties in the medical management including optimal pain control.

Pain in a patient with SBS is multifactorial and can have varying components of visceral, somatic, and functional pain. Pain in patients with SBS may be secondary to the underlying disease or its long-term complications. The source of pain cannot often be pin pointed to one cause. Pain can be due to residual disease such as inflammation, strictures, adhesions, or partial small bowel obstruction in Crohn's disease,

radiation enteritis, or chronic mesenteric ischemia [10]. Patients who undergo sequential multiple resections and laparotomies often suffer from chronic pain. Patients with SBS are dependent on Total Parenteral Nutrition (TPN) and require central venous access in order to receive TPN. Numerous complications are associated with TPN as well as central lines, including infections, thrombosis, liver steatosis. Fat malabsorption can lead to deficiency of Vitamin B12 and neuropathic pain.

Patients with residual Inflammatory bowel disease (IBD) Crohn's disease are more predisposed to develop Irritable bowel syndrome (IBS) which can have profound effect on the psyche of the patient [10]. Multiple prolonged hospitalizations can predispose to depression and mood disorders.

Pain pathways involve stimulation of nociceptors which in turn activate second order neurons in the spinal cord leading to transmission of neural signals to higher centers in brain stem and cortex resulting in perception of pain [10]. Visceral nociceptive receptors are unique in a way that they recruit large sections of the central nervous system, resulting in the diffuse, poorly localized, and often referred nature of visceral pain [10]. Parietal peritoneal inflammation presents as somatic pain which is well localized [11]. Changes in sensitivity of afferent neurons can lead to persistent pain [11].

33.3 Pain due to Kidney Stones

Renal function may be impaired in SBS patients with an intact colon secondary to calcium oxalate nephrolithiasis [12]. Dietary oxalate is normally bound to intraluminal calcium and excreted in the stool. In SBS patients with intact colons and fat malabsorption, calcium binds to unabsorbed fatty acids in the lumen, leaving oxalate free to pass into the colon to be absorbed by the bloodstream and filtered by the kidneys. In the kidneys, oxalate binds to calcium causing oxalate nephrolithiasis and the risk of progressive obstructive nephropathy [13]. Obstructive nephropathy can lead to pain and the resulting kidney dysfunction may necessitate dose alteration of certain medications used to treat pain.

33.4 Pain due to Hepatobiliary Dysfunction

Patients may experience abdominal pain secondary to hepatobiliary complications including steatosis, cholestasis, or cholelithiasis. These complications may occur from the altered bowel anatomy or from the parenteral nutrition often required as part of treatment. The administration of >1 g/kg/day of parenteral lipids conjointly with chronic cholestasis is associated with the development of liver disease. It is important for the pain practitioner to be aware of this complication while devising a treatment plan as medications may need to be altered based on the presence of liver dysfunction [14]. End stage liver disease also leads to impaired coagulation which

becomes important for pain procedures such as neuraxial techniques, regional nerve blocks, neuromodulation procedures such as spinal cord stimulators and placement of intrathecal pumps.

Cholelithiasis can occur in up to 40% of adults with SBS. Biliary sludge is even more common. Decreased concentration of bile acids secondary to altered enterohepatic circulation is the predominant cause of stone formation. Gallbladder stasis due to decreased cholecystokinin secretion in patients with limited enteral intake can also contribute. These conditions can contribute to pain in patients with SBS. The risk for cholelithiasis increases significantly if less than 120 cm of intestine remains after resection, if the terminal ileum has been resected, and if the patient is on TPN [2]. End-stage liver disease develops in about 15% of patients on long-term TPN [2]. In fact, patients who are evaluated for bowel transplant are often evaluated for concomitant liver transplant if the degree of liver dysfunction is significant.

33.5 Bone Pain

Malabsorption of fat-soluble vitamins predisposes to osteoporosis which can predispose to fractures and hence bone pain.

33.6 Absorption of Pain Medications

Enteric absorption of orally administered anti pain medications is variable and depends on a number of complex factors. Oral bioavailability of drugs depends on the physical characteristics of the drug as well as patient factors [15]. Characteristics of the drugs include factors such as molecular weight, physical form such as capsule or syrup, enteric coating, inert substances, and lipid solubility [15]. Decreased intestinal length, however can have a profound impact on both pharmacokinetics and bioavailability of oral medications [15]. Most drug absorption occurs in the upper small intestine where long villi increase the surface area. In addition, the upper small intestine has high blood flow and a favorable pH for drug absorption [16].

The surface area of the lumen of the small intestine is the most significant factor on drug absorption. Therefore, if the length of the small intestine has been reduced, drug absorption can be impacted to varying degrees. Patients, who have undergone small intestine stomas (jejunostomy or ileostomy) may have alterations in drug absorption based on the length of residual small intestine. Adult bowel lengths differ thus, it is always important to quantify the remaining functional bowel versus any resected/non-functional bowel lengths [16].

The large intestine has less of an impact on drug absorption. Patients with a colostomy are unlikely to suffer from significant alterations in drug absorption since as discussed above most drugs are absorbed in the small intestine. Despite the possibility of undissolved drugs in the stoma, the stoma is typically not the predominant

factor in decreased drug absorption. Typically, normal doses and formulations of drugs can be used in most of these patients. However, capsules can be replaced by liquid formulations, if available for psychological reasons.

Absorption, however, can also be impaired by deficient integrity of the underlying mucosa. Crohn's disease, in particular, can lead to active inflammation and creation of strictures. Inflammation can reduce villi contact and luminal permeability [16]. Strictures can decrease passage of pills since they may not be able to pass the point of the stricture.

33.7 Diagnosis

The signs and symptoms of SBS can vary greatly depending due to the heterogeneity of the disorder. It is important to recognize that patients may present with different symptoms. This chapter will focus on the adult population as clinical manifestations in the pediatric population may differ. Patients with SBS may complain of abdominal pain, bloating and cramps. Diarrhea is common. In case of liver problems as described in pathophysiology, easy bruising, ascites, signs of advanced liver failure can be seen.

A comprehensive assessment should start with a complete history and physical exam. Site and nature of pain along with duration and radiation should be noted. Pain is often related to the underlying etiology however, it is important to rule out residual disease and more serious complications and sequelae for the precipitating disease process. A plain film of the abdomen can rule out perforation. Leukocytosis is present in infections at the site of central lines, abscess formation in the abdomen, or residual inflammation in the small bowel as in Crohn's disease. Neuropathic pain should prompt an evaluation for vitamin B12 deficiency, especially in a patient who has undergone a large resection of ilium [10]. Endoscopy in form of colonoscopy or upper endoscopy will be necessary to confirm evidence of residual disease [10]. Evaluation of obstruction as well as strictures require small bowel imaging [10]. Radiologic assessment as in CT scan or MRIs may be needed to find an organic cause of pain. Small-bowel imaging is often necessary to identify strictures or adhesions that can be insidious sources of pain. It is important to know liver function when prescribing new medications as a number of analgesic medications are metabolized by the liver. When an intervention procedure is planned, coagulation parameters should be evaluated pre procedure.

33.8 Treatment

Short Bowel Syndrome is a challenging condition and demands a dedicated multidisciplinary team effort to overcome the morbidity and mortality in these patients [2]. Uncontrolled pain often leads to anxiety [10].

In general, the principles of medication administration are derived from the pathophysiological changes in oral medication absorption. Higher doses are typically needed, intravenous (IV) formulations are sometimes necessary, and delayed- or extended-release medications should generally be avoided [17].

33.9 Non-pharmacological Pain Management

Most of the nonpharmacologic interventions used for management of abdominal pain have been used in patients specifically for Irritable bowel syndrome (IBS) and Inflammatory bowel disease (IBD) such as Crohn's disease. IBD is a major causative factor for SBS, therefore it is prudent to use these therapies in patients with SBS. Non pharmacological interventions include cognitive behavioral psychotherapy, medical hypnosis, mindfulness meditation, and stress management [10, 18, 19].

Cognitive behavioral therapy (CBT) is an intervention which helps a patient to recognize his/her negative thoughts and modify them to feel that he/she has control and can be more responsible for reducing his/her pain. CBT has shown promising results in patients with functional GI pain [11, 18].

Medical hypnosis and mindfulness meditation helps with relaxation and better coping mechanism with pain [18]. Gut directed hypnotherapy involves teaching the patient relaxation, ego strengthening and coping skills [19]. Body Awareness therapy consists of simple movements that help the body find its natural posture [19].

33.10 Pharmacological Management

Malabsorption of medications which depend on enterohepatic circulation should be kept in mind when prescribing oral medications [20]. It is recommended to avoid sustained-release or enteric-coated formulations due to altered motility of the gut. Alternate routes of administration of medications such as transdermal, sublingual, rectal, subcutaneous, intramuscular or intravenous should be considered. Rectal and sublingual administration of drugs is easy and the bioavailability is better than oral route as the absorbed drug bypasses the first pass metabolism [21]. However, rectal route may not be preferred by the patient. Therefore, any management plan should include the patient's comfort with handling the medication (Table 33.1).

Medications used for symptom relief of SBS are antisecretory and antimotility agents. They are often necessary to control gastric hypersecretion and high-volume diarrhea. One of the most distressing symptoms for the patient with SBS is diarrhea. Gastric hypersecretion leads to diarrhea which is common in the postoperative period. Anti-secretory agents include—Histamine-2 blockers, Proton pump inhibitors, cholestyramine, octreotide, and clonidine [2, 11, 22]. Opiates have been the mainstay of therapy for the control of diarrhea [23]. Loperamide in doses of 4–16 mg daily or even double these doses, has been used. However, higher doses

Table 33.1 Factors affecting oral absorption include: [22]

• The change to the total surface area, permeability, and integrity of the intestinal epithelia
• The change in orocecal transit time
• The impact on dissolution and release of the drug from the formulation
• Loss of the specific absorptive area in the bowel where the medication is routinely absorbed
• Loss of specific enzymes or epithelial transport proteins needed to activate the drug
• The location of the bowel that acts as the site of action for the medication
• The health of the remaining bowel
• The magnitude of intestinal adaptation
• Other conditions that alter intestinal architecture and lead to impaired absorption (eg, small bowel bacterial overgrowth)

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than usual may need to be given as the enterohepatic circulation of loperamide is disrupted [20]. Codeine has also been used for control of diarrhea however, the side effects of sedation and nausea can limit its use [23]. Transdermal clonidine has also shown a significant reduction in fluid losses and symptomatic control of diarrhea [2, 24]. Anti spasmodics—anticholinergic drugs such as Hyoscyamine and Dicyclomine are used to relieve spasmodic pain from inflammation or partial obstruction.

Medications that can be used for acute pain in a patient with SBS include: [10]

1. Acetaminophen–Acetaminophen is a component of multimodal regimen and is available Over the counter. It is commonly used as the first line drug for treatment of pain in acute setting. Oral acetaminophen is absorbed primarily from jejunum [21]. Acetaminophen is also available as rectal suppository and intravenous formulation. Although it is not as effective as NSAIDs for pain control, the safety profile is much better and does not lead to adverse effects involving the gastro intestinal tract. This is favorable in patients who are not able to tolerate oral intake as rectal acetaminophen can be used at home and has no abuse potential as compared to opioids. However, it should be used with caution in patient with end stage liver disease as a sequelae of SBS.
2. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are a family of drugs particularly effective in controlling inflammatory pain. They inhibit the production of prostaglandins by cyclooxygenase (COX) enzymes [10]. There are concerns with use of NSAIDs in patients with bowel inflammation due to inhibition of COX-1 and 2 enzymes which maintain the mucosal integrity of the intestine [25]. Patients with SBS are often dehydrated due to diarrhea and high ostomy output. NSAIDs should therefore be used with caution to prevent kidney damage if there is a suspicion for dehydration. However, NSAIDs still remain a component of multi-model regimens for short term pain control especially in the acute post-operative setting and the majority of patients do not develop clinical worsening of IBD [25]. Diclofenac is completely absorbed in the colon and can be useful in pain management especially in the acute postoperative period [21]. Indomethacin and diclofenac are also available in suppository form [21, 26].

Oral Aspirin has been shown to be effectively absorbed with 30 cm of small intestine with an intact colon or only 35 cm of small intestine alone [27].

3. Opioids—Opioids have been the mainstay for the treatment cancer pain and motility control [10]. However, they have not been as effective in treating functional as well as chronic GI pain [28]. All oral formulations of opioids are absorbed through the small intestine. The implications of reduced intestinal length theoretically predispose to altered absorption. However, in clinical practice, most of the opioids are reasonably absorbed even with reduced intestinal length. However, in patients who are unable to tolerate oral drugs, alternate routes are available for a number of drugs. Fentanyl and buprenorphine are available as a transdermal patch. This can be useful in a patient with SBS as the enteral absorption is bypassed and can be used when the patient is not allowed to take medications by mouth. Slow release of medication also prevents abuse potential as the dopamine surge is diminished. Methadone, oxycodone, morphine, and hydromorphone are available as sublingual preparations. The drug is directly absorbed into the systemic circulation bypassing the first pass metabolism. Methadone is absorbed primarily in the stomach with little absorption occurring beyond the pylorus. Since patients with SBS usually have an intact stomach, methadone may be a good choice can be for patients with chronic pain. Adverse effects of opioid use that can be particularly dangerous in SBS include, toxic megacolon, narcotic bowel syndrome, and addiction or abuse [10]. Patients with SBS are often in pain and are prescribed narcotics for visceral pain which is not helpful. Over the course of time, these patients become dependent on narcotics. Narcotic bowel syndrome is opioid induced chronic abdominal pain that worsens with increasing doses of opioids [28]. The use of opioids should be used for acute post-surgical pain and the treatment of diarrhea and not chronic abdominal pain.

Patients with SBS often suffer from chronic pain conditions as described above and hence there is a role of analgesic adjuvants in managing chronic pain. In addition to pain, patients often suffer from depression which sometimes is more troublesome due to prolonged hospitalization and multiple surgeries. Patients with IBD often develop IBS which has been shown to have a psychological component. The following classes of drugs have been used in chronic pain conditions such as neuropathic pain syndromes and other persistent pain conditions such as fibromyalgia.

1. Tricyclic antidepressants (TCAs) have anti-depressant effects and are a useful adjunct in treatment of chronic pain due to their noradrenergic action [28, 29]. TCAs are commonly prescribed to chronic persistent pain patients. They can have significant anticholinergic and antihistaminic side effects which include, dry mouth, dizziness, sedation, weight gain [10, 28]. Secondary amine TCAs (e.g., desipramine, nortriptyline) are better tolerated than tertiary amine agents (e.g., amitriptyline, imipramine) [28]. Patients with SBS are prone to depression and psychological problems due to a number of issues which include altered body function and appearance and dependence on TPN for survival [29]. Amitriptyline is extensively absorbed through the stomach and small intestine

and is hepatically metabolized to nortriptyline. Oral absorption is >95% [30]. Amitriptyline has been used successfully for treatment of depression and chronic epigastric pain in patients dependent on TPN. The powder form of the drug has exhibited good buccal absorption [29]. A patient dependent on TPN who was unable to tolerate amitriptyline showed good oral bioavailability of nortriptyline [31].

2. Selective Serotonin Reuptake Inhibitors (SSRIs)—Escitalopram, Fluoxetine, Paroxetine, Sertraline (all require adjustment in liver disease) help in the management of associated depression, but are not generally effective in the management of acute pain [10, 28]. SSRIs are useful adjuncts for the treatment of co-morbid depression. Escitalopram and citalopram can be given orally to patients with 180 cm of small intestine or 80 cm of small intestine and 50% of remaining colon [32]. Fluoxetine has been administered successfully via the sublingual route [33]. Transdermal administration of antidepressant drugs, including fluoxetine, amitriptyline, and doxepin, has been described in the literature [33].
3. Serotonin—Noradrenergic Reuptake Inhibitors (SNRI) provide pain relief via its noradrenergic action [28]. Duloxetine (Cymbalta) is commonly used in chronic pain conditions as an adjuvant. It is mainly absorbed in the duodenum so can be given safely to patients with SBS with intact duodenum.
4. Anticonvulsants—Gabapentin, Pregabalin are calcium channel blockers that have been used to treat neuropathic and visceral pain [28]. Gabapentin is absorbed in the upper small intestine. Pregabalin is absorbed throughout the small intestine as well as parts of colon. Therefore, Pregabalin may be preferred in patients with SBS with neuropathic pain over Gabapentin.
5. Muscle relaxants such as Baclofen are absorbed in the small intestine. Tizanidine is a centrally acting alpha 2 agonist, used for muscle spasms. Liver function should be monitored in patients on Tizanidine.
6. Ketamine is an *N* Methyl D Aspartate antagonist that has been used successfully in patients with chronic regional pain syndrome (CRPS) as well as acute pain conditions. Ketamine is available as an intravenous (IV) and oral preparation. Thus, the IV form may be considered in managing acute or chronic pain conditions in patients with SBS.
7. Lidocaine. IV lidocaine is an amino-amide local anesthetic that has been found to have analgesic and anti-inflammatory properties. Studies suggest that IV lidocaine may be a useful analgesic in the post-operative period particularly after laparoscopic abdominal surgery, thus it may be a good choice in patients who have undergone bowel resection [34].

Patients with strictures and adhesions leading to bowel obstruction generally require surgical intervention.

Procedural intervention in acute pain conditions—Management strategies in acute pain conditions should include neuraxial and regional techniques if coagulation parameters permit. The severity of liver dysfunction should be taken into account for total dose of the local anesthetics. Advantages of neuraxial and regional

techniques include limiting the amount of narcotic and other pain medications as well as better pain control without much systemic effects.

In emergency situations such as acute abdomen, where oral intake of medications is contraindicated, parenteral route should be utilized. Patient Controlled Analgesia for intra venous drugs should employed in such situations. However, every effort should be made to transition to oral and other routes of drug delivery as soon as possible. Oral medications frequently employed include hydromorphone, oxycodone, and morphine. Methadone can be a reasonable choice in patients who are opioid dependent as it is primarily absorbed through the stomach.

33.11 Pain Assessment Tools

Abdominal pain in the hospital can be assessed with commonly used pain scales such as the Visual Analog Scale and Numeric Rating Scale. Both these commonly used tools measure pain on a scale of 0–10 [18]. The severity of abdominal pain in IBS, such as Crohn's disease, has been measured using The Visceral Sensitivity Index [18]. The Brief Pain Inventory (BPI) measures pain severity and interference of pain with functional ability of the patient including activity, mood, walking ability, sleep, and enjoyment of life. The McGill Pain Questionnaire provides information regarding the intensity as well as the qualitative description of the pain (eg, burning vs stabbing) [18].

33.11.1 Challenges in Management of Pain While in the Hospital

- Unreliable oral absorption of drugs
- Oral route may not be available
- Opioid dependence is an issue
- Psychological factors are often more challenging to manage

33.11.2 Management of Pain in the Inpatient Setting

Formulating a treatment plan for a patient with SBS may be challenging. It is best to rely on a multimodal treatment strategy that includes non-pharmacologic modalities, regional anesthesia if applicable, and pharmacologic management. One needs to do a careful assessment of the patient's remaining functional GI tract in order to best optimize the treatment course. In general, for mild to moderate pain acetaminophen may be the medication of choice. NSAIDS particularly, Diclofenac can be considered in the absence of renal dysfunction. For moderate to severe pain,

opioid can be considered especially in the acute setting. Non-oral formulations should be considered in the acute setting as decreased absorption may occur with oral routes. When transitioning to oral formulations, consider utilizing liquid or sublingual formulations. Recognize that oral formulation may require higher dosing regimens.

In addition, ketamine or lidocaine infusions may be utilized in the acute in-patient setting. Adjuvant medications can also be considered. Pregabalin may be more effective than Gabapentin when treating neuropathic pain secondary to its absorption profile as discussed earlier in this chapter. Non-pharmacologic modalities such as physical therapy, cognitive behavioral therapy, yoga, and acupuncture can be initiated in the in-patient setting. It is important to formulate a plan in conjunction with the patient to optimize chances of success.

33.12 Discharge Plan for Pain Management

The patient should be involved in the discharge planning for pain management. Proper education is paramount. Continuation of non-pharmacological strategies are of utmost importance. Oral medications can be utilized but the patient may need frequent monitoring to assess their efficacy in light of the variable absorption that can occur. At times, higher doses of medications that rely on the small intestine for absorption may be required. Use alternative (non-oral) formulations of medications if possible. Liquid medications might also be advantageous especially in patients with stomas. Recognize that in the palliative setting, patients with SBS may discharged on PCAs if warranted. Although complicated, a well-planned treatment plan can be developed it order to maximize the patient's pain relief.

33.13 Summary

- Remember that each patient with SBS should be managed as an individual. Patients have different symptoms, remaining functional bowel lengths, and psychological characteristics that necessitate an individualized approach to care.
- Work up must begin with a thorough history and physical
- Utilize laboratory testing or imaging if necessary, to delineate any sequalae of SBS.
- The treatment plan should be discussed with the entire treating team.
- The patient should be informed of advantages and disadvantages of each treatment modality.
- Conservative modalities should be utilized first line. Treatment can then be escalated if the patient does not respond or reports moderate to severe pain.
- Safe modalities and medications—use of adjuncts such as TCAs, SNRIs, and acetaminophen if no liver dysfunction

  - If there is no contraindication to use of regional or neuraxial techniques, every effort should be made to use peripheral nerve catheters or epidural catheters for pain control as these avoid the enteral use of drugs as well as minimize the adverse effects as detailed above.

- Opioids—May be utilized. May need to initially consider non-oral formulations. Always use lowest possible effective dose but recognize that oral formulations may require higher dosing as a consequence of decreased absorption. Monitor diligently for signs and symptoms of opioid abuse or addiction.
- Modalities and Medications to avoid: neuraxial techniques when there is evidence of active infection or altered coagulation and long term NSAIDs especially in patients with Crohn's.

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Chapter 34
Incidentally Identified Opioid Misuse and Opioid Use Disorder While Inpatient

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34.1 Introduction

Nearly 20% of hospitalized patients have a substance use disorder (SUD) [1, 2]. Opioid use disorder (OUD) is commonly encountered in hospitalized patients with increasing prevalence amongst the opioid epidemic. Over two million individuals meet criteria for OUD and ten million people misused opioids in the past year [3]. Hospitalized patients with OUD are more likely to have negative medical outcomes and leave without completing treatment against medical advice [4].

Patients may not disclose ongoing substance use while inpatient for various reasons including fear of stigmatization and unforeseen consequences. Providers must be equipped to address OUD while inpatient and reduce these fears of stigmatization through reassurance that disclosure of substance use will not negatively impact medical care. Comprehensive evaluations and screening for OUD or other SUDs should be done in a nondiscriminatory manner and with intent of optimizing medical care and providing evidence-based OUD treatment.

Initiating evidence-based treatment for OUD in the acute hospital setting is feasible and effective [5–9] and results in better medical and substance use disorder outcomes [6, 8]. Currently there are three FDA-approved medications for OUD: methadone, buprenorphine, and extended-release injectable naltrexone. All patients with OUD not on pharmacologic management should be recommended one of these treatment options while inpatient and connected with outpatient substance use treatment [10–13]. Without substance use treatment, the majority of individuals will return to substance use upon discharge and are at

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high risk for poor outcomes and opioid overdose [14, 15]. Engaging patients in treatment for OUD while inpatient improves outcomes for some of the highest risk individuals [7].

This chapter will review best management strategies for identifying opioid misuse or OUD, opioid overdose, acute withdrawal, initiating medications for opioid use disorder (MOUD) while inpatient, and connecting inpatients with substance use treatment prior to discharge.

34.2 Why Do Patients Not Disclose Substance Use?

Patients may decide to not disclose substance use for various reasons. Patients with SUDs may expect to be treated negatively by healthcare providers based on previous experiences in medical settings. They may withhold information from providers for fear of stigmatization, negative reactions, and unforeseen consequences. These fears are not unfounded as studies have shown that providers often possess negative attitudes and feel ill equipped in managing patients with SUDs [16–22].

Patients may also have concerns about confidentiality of the medical record and disclosure of substance use potentially impacting their job, insurance payments, medical care, and providers' willingness to prescribe some medications including controlled substances such as opioid analgesics for pain conditions [16]. For instance, patients with opioid use disorder (OUD) on opioid agonist treatment (methadone or buprenorphine) fear a reduction in dosing or that their pain will be undertreated in an acute medical setting [20, 21]. This is often based on previous interactions with providers who believe prescribing opioids for pain will increase the risk of relapse or worsen addiction [23, 24]. There is no evidence that exposure to opioid analgesics in the presence of pain increases relapse in patients on opioid agonist treatment [20, 25, 26]. Patients are more likely to relapse or access opioids analgesics from external sources when their pain is undertreated, and may resort to illicit substance use while inpatient [27, 28].

Aside from fear of stigmatization, patients may not be ready to disclose substance use, accept diagnosis of a SUD, or be motivated to start treatment. Motivation to change substance use behavior is an important component of the recovery process and therapeutic interventions exist to enhance motivation such as motivational interviewing [29]. In some cases, hospitalized patients may use substances to avoid acute withdrawal and do not disclose this to their provider. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) characterizes a substance use disorder by a pronounced craving and preoccupation for the substance, inability to refrain from using it, and escalation of use despite negative consequences [30]. Patients that do not disclose opioid use carry risk for overdose while inpatient. Those at greatest risk are perhaps those who do not disclose prior opioid use and are not using opioids while inpatient. These individuals have decreased tolerance and are at increased risk of opioid overdose upon discharge [12].

Providers can reduce fear of stigmatization through reassurance that disclosure of substance use will not negatively impact medical care or prevent adequate pain management. History-taking and screening for SUDs should be done in a nondiscriminatory manner and with intent of optimizing medical care and providing evidence-based SUD treatment. Choice of substance use treatment, in particular initiating medication for opioid use disorder (MOUD), should be a shared decision between the patient and clinician. MOUD includes buprenorphine, methadone, and extended-release injectable naltrexone. More providers should be trained in screening for SUDs and delivering treatment so that providers feel more equipped to manage patients with SUDs and have improved attitudes overall [11, 12].

34.3 Management of Acute Opioid Withdrawal

34.3.1 Opioid Withdrawal Syndrome

Opioid withdrawal syndrome refers to a range of symptoms that occur after stopping or dramatically reducing the dose of opioids after prolonged use. Opioid withdrawal symptoms include mydriasis, lacrimation, rhinorrhea, diaphoresis, nausea, vomiting, abdominal cramps, diarrhea, piloerection, muscle pain, and anxiety [10, 13]. Common signs of opioid withdrawal can be seen in Table 34.1. Withdrawal symptoms emerge within 12 h of the last dose of short-acting opioids such as heroin and within 30 h of the last long-acting opioid such as extended-release oxycodone. Withdrawal symptoms generally persist anywhere from 3 to 5 days for short-acting opioids and 10 days for long-acting opioids [13]. The duration of withdrawal symptoms can be influenced by patient factors including age, duration of opioid exposure, type of opioid, physical condition and medical comorbidities [12].

Withdrawal states can be particularly challenging for patients with comorbid psychiatric and pain conditions. Patients with comorbid psychiatric disorders in

Table 34.1 Common signs of opioid intoxication and withdrawal [10–13]

Intoxication signs	Withdrawal signs
Miosis	Mydriasis
Bradycardia	Tachycardia
Hypokinesis	Hyperreflexia
Decreased respiratory rate	Increased respiratory rate
Calmness	Anxiety, dysphoria, irritability
Sedation	Lacrimation
Head nodding	Rhinorrhea
Slurred speech	Diaphoresis
	Abdominal cramps, nausea, vomiting, diarrhea
	Muscle aches

opioid withdrawal may experience an exacerbation of psychiatric symptoms such as dysphoria, anxiety, difficulty sleeping, suicidality, and irritability [12, 13]. Patients with comorbid pain conditions may experience worsening pain when in opioid withdrawal and request additional pain medication. Distinguishing between pain from a pre-existing condition and pain related to opioid withdrawal can be difficult. Clinicians must correlate perceived pain with diagnostic work-up and clinical findings related to medical condition, as well as duration and quantity of opioid use prior to hospitalization [11].

Opioid withdrawal states may be spontaneous or precipitated by medication. Spontaneous withdrawal occurs with cessation of opioid use or dramatic reduction in opioid dosing. Precipitated withdrawal states can occur when an opioid-tolerant patient receives an opioid antagonist (naloxone or naltrexone) or the partial opioid agonist buprenorphine. Buprenorphine has a high affinity for the mu-opioid receptor relative to other opioids and can precipitate withdrawal. Precipitated opioid withdrawal states can be severe and require further inpatient management, particularly in cases where fentanyl and other high potency synthetic analogs are in heroin supplies. The time for maximal precipitated withdrawal occurs varies between agents and can be seen in Table 34.2 [12].

There are various clinical scenarios where an inpatient may enter an opioid withdrawal state and several examples are listed in Table 34.3. Many opioid-tolerant patients administered naloxone will enter an acute opioid withdrawal state that requires management. Patients admitted medically with opioid use disorder may be interested in starting buprenorphine prior to discharge and will need to enter a state of mild-moderate opioid withdrawal before induction. Opioid use outside of the hospital might be difficult to quantify for some patients, increasing risk of both withdrawal and overdose. In cases where a patient is incidentally found to be in

Table 34.2 Time of maximal precipitated withdrawal for different agents [12]

Agent	Time
Naloxone (IV, IN)	1–2 min
Naloxone (IM)	3–5 min
Buprenorphine (sublingual)	Up to 90 min
Extended-release injectable naltrexone (Vivitrol®)	Up to several hours

Table 34.3 Clinical examples in which a patient may need opioid withdrawal management

Emergency rescue from opioid overdose with naloxone and subsequent medical management
Opioid-induced hyperalgesia and patient needs alternate pain management strategies
Patient with opioid use disorder medically admitted requesting to be off opioids and receive opioid antagonist treatment (Vivitrol®) prior to discharge
Patient with opioid use disorder experiencing mild-moderate opioid withdrawal prior to buprenorphine induction
Patient with opioid use disorder medically admitted on unknown quantity of opioids outside the hospital or potentially minimizing use and experiencing withdrawal

acute opioid withdrawal without prior report of opioid-dependence, a thorough evaluation and history should be obtained before starting opioid agonists. This also presents the opportunity to engage patients with OUD in treatment and potentially start MOUD while inpatient. Initiating MOUD is discussed in further detail in this chapter.

Opioid withdrawal is rarely life threatening but if untreated can lead to negative patient outcomes. Patients may leave against medical advice to obtain opioids to treat the withdrawal or succumb to opioid cravings [31]. These patients are at risk for poor medical outcomes with abbreviated medical intervention. The opportunity to engage the patient in treatment for OUD and start pharmacotherapy is also lost in these settings. Opioid withdrawal management is critical in mitigating risk for negative medical sequelae, opioid overdose, and death. Opioid withdrawal management alone though is not considered effective treatment of opioid use disorder given high rate of relapse [32]. Patients should be offered standard treatment with MOUD and be connected with outpatient providers and appropriate psychosocial interventions.

34.3.2 Assessment of Opioid Withdrawal

Assessment of a patient in opioid withdrawal should include a comprehensive medical history and physical examination. There are scales to assess opioid withdrawal listed below. Objective signs are more reliable than subjective when available, although both are valuable and can be done in conjunction. These scales can be administered on initial assessment and intermittently when treating opioid withdrawal [10–12].

1. Objective Opioid Withdrawal Scale (OOWS) is an objective measure where the clinician assesses for 13 signs of opioid withdrawal [33].
2. Clinical Opioid Withdrawal Scale (COWS) is a clinical assessment for 11 medical signs of opioid withdrawal [34].
3. Subjective Opioid Withdrawal Scale (SOWS) is a measure of 16 subjective symptoms of withdrawal reported by the patient on a five-point scale [33].

34.3.3 Medications in Opioid Withdrawal

Withdrawal symptoms can be managed with alpha-2 adrenergic agonists (clonidine, lofexidine, and dexmeditomidine), antidiarrheal medications, anxiolytics, and sleep aids [10–12]. Opioid agonists can be administered or standing opioid doses increased to target withdrawal symptoms. Clinical judgment and objective assessment of withdrawal symptoms is recommended before adjusting opioid regimen or

considering initiation of an opioid agonist (methadone or buprenorphine) for dual management of pain and OUD. Referral to a pharmacologically managed detoxification program may be needed following inpatient medical hospitalization.

34.3.3.1 Opioid Agonists

Methadone and buprenorphine are both recommended in opioid withdrawal management. The use of either is more complex in inpatient cases with OUD on concurrent acute pain management regimens. Patients on standing opioids other than buprenorphine or methadone for pain incidentally found to have OUD should be transitioned to MOUD when feasible.

If a patient is already on methadone or buprenorphine, dosing can be adjusted to target opioid withdrawal symptoms and pain concurrently. For patients on methadone for pain and with comorbid OUD, they must be connected with a federally certified opioid treatment program that will provide methadone, which can also be a barrier to treatment if spots are unavailable at the time of discharge. Additionally, these programs often request collaboration in dosing protocols to assure seamless transition to starting doses at the methadone clinic. For patients on buprenorphine for pain and with comorbid OUD, they must be connected with an outpatient provider that has the special waiver to prescribe buprenorphine for OUD. Patients may decline initiation of opioid agonist therapy for comorbid OUD while inpatient and acute withdrawal can be managed with opioid agonists or adjustment in standing opioid regimens as needed per clinical assessments during inpatient stay.

For patients not on standing opioids already, buprenorphine can be started 12–18 h after the last dose of a short-acting opioid such as heroin and 24–48 h after the last dose of a long-acting opioid such as extended-release oxycodone [10]. A dose ranging 4–16 mg per day is generally sufficient to suppress withdrawal symptoms and can be tapered if patient declines to continue as MOUD [10–13]. Buprenorphine doses may be higher in settings where a patient has used heroin with fentanyl or other high potency synthetic analogs. Methadone can be started in doses ranging 20–30 mg per day. Patients that decline continuation of either opioid agonist should be assessed for appropriateness of discharge to outpatient provider versus referral to detoxification program or substance use rehabilitation program [10–13].

34.3.3.2 Alpha-2 Adrenergic Agonists

A hallmark feature of opioid withdrawal is the hyperexcitability of the nervous system. Alpha-2 adrenergic agonists directly combat the enhanced noradrenergic tone and are effective in alleviating withdrawal symptoms [35]. Both clonidine and lofexidine are effective in managing opioid withdrawal symptoms. Clonidine has been used off-label for opioid withdrawal management in the United States for years. Lofexidine has been long available in Europe for opioid withdrawal, but only

recently approved in the United States in 2018. Lofexidine has a better safety profile and less hypotensive effects than clonidine [36, 37].

Clonidine is generally started at 0.1 mg every 4–6 h for opioid withdrawal and can be increased 0.1–0.2 mg per day up to a maximum of 1.2 mg per day. Lofexidine is started at 0.54 mg every 5–6 h and the dose can be increased daily based on symptoms up to a maximum of 2 mg per day [10, 37]. While administering alpha-2 agonists, blood pressure and heart rate should be closely monitored. Alpha-2 agonists may cause dose-dependent reductions in heart rate and may enhance the AV-blocking effect of beta-blockers. Sinus node dysfunction may also be enhanced [37]. Baseline and regular monitoring of EKG is recommended with risk for QT prolongation, particularly if dosed in conjunction with other QT prolonging agents such as methadone.

Both clonidine and lofexidine are primarily metabolized via the cytochrome P450-2D6 (CYP2D6) enzyme. Medications that inhibit CYP2D6 such as the antidepressant paroxetine can increase the patient's exposure to lofexidine by as much as 28% and may exacerbate side effects of bradycardia or orthostatic hypotension [38]. Alpha-2 agonists should be tapered and dose decreased gradually before discontinuation to avoid rebound hypertension. Not all opioid withdrawal symptoms are alleviated with alpha-2 agonists and other medications may be indicated [10].

34.3.3.3 Other Medications

Other medications may be needed to alleviate opioid withdrawal symptoms. Benzodiazepines and other anxiolytics can be administered for anxiety. Caution should be used with benzodiazepine dosing in patients with a history of benzodiazepine use disorder and benzodiazepine withdrawal symptoms differentiated from opioid withdrawal symptoms (tremor and more autonomic hyperactivity). Loperamide can be used for diarrhea and ondansetron for nausea or vomiting. Non-opioid analgesics such as acetaminophen and nonsteroidal anti-inflammatory agents (NSAIDs) can be used for muscle aches. Many of these agents cause QT prolongation (ondansetron, alpha2-adrenergic agonists) and regular EKG monitoring is needed particularly in conjunction with other QT-prolonging agents [10–13].

34.3.4 Opioid Withdrawal in NPO Patients

In certain circumstances, opioid withdrawal will need to be managed in patients not tolerating oral medications. This could be patients with gastrointestinal pathology, upcoming surgery, or impaired mental status. Both methadone and buprenorphine are available as intravenous formulations. Additionally, there is some although limited research supporting use of transdermal clonidine and intravenous dexmedetomidine. Further research will need to be done to determine ideal dosages. Studies done on dexmedetomidine have used doses ranging from 0.5 to 1.4 mcg/kg/h [39].

34.3.5 Anesthesia-Assisted Withdrawal Management

Rapid opioid detoxification with opioid antagonist induction using general anesthesia uses large doses of naloxone to precipitate acute opioid withdrawal. Patients are under general anesthesia and may experience mild withdrawal symptoms for about 6 days upon awakening compared with similar withdrawal symptoms on a 20-day methadone taper [40, 41]. Anesthesia-assisted rapid opioid detoxification is not recommended due to serious complications including cardiac arrest and death [10, 42]. A systematic review of five randomized trials concluded lack of benefit, potential serious harms, and high costs for anesthesia-assisted rapid opioid detoxification [43].

34.4 Management of Acute Opioid Overdose

34.4.1 Presentation

Acute opioid overdose is one of the major concerns when treating a patient found to be using illicit opioids while admitted to the hospital. Miosis, stupor, and respiratory depression are signs suggestive of opioid overdose. Of these the most reliable and most correlated to the need for acute treatment is respiratory depression. Stupor and miosis both have poor specificity. In fact, patient with opioid overdose may have mydriasis in the setting of using multiple other substances [44]. In a monitored setting, the presenting sign of overdose is often hypoxia. In an unmonitored setting, patients may present with varying levels of sedation including comatose and unresponsive.

34.4.2 Naloxone

Naloxone is a competitive opioid mu-receptor antagonist used as an antidote for opioid overdose. In the hospital setting, parenteral administration is often the preferred route although it is also available as intranasal and inhalational formulations. Onset of action is less than 2 min and duration of action is between 20 and 90 min. In patients with opioid tolerance, initial plasma levels are lower and volume of distribution is greater leading to slower onset and longer duration [44].

34.4.3 Acute Management

Initial management of a patient with concern for opioid overdose is supportive. The primary pathophysiology is hypoventilation leading to hypercarbia and hypoxia. Patient should be ventilated with a bag-valve mask with goals to achieve normocarbia and adequate oxygen saturation.

The initial dose of naloxone is 0.04 mg intravenously with a repeat dose of 0.5 mg after 2–3 min if patient does not respond. Subsequent doses after patient responds should be titrated to prevent respiratory depression without precipitating withdrawal in opioid-tolerant patients and/or uncontrolled pain in patients being treated for acute pain. Despite these concerns, priority should be given to ensuring adequate reversal of opioid effects as opioid withdrawal symptoms are rarely life-threatening. Common withdrawal symptoms include diaphoresis, myalgias, vomiting, and diarrhea. The precise dose required depends on the dose and affinity of the competing opioid [44].

34.4.4 Recurrent Respiratory Depression

Patients are at risk for recurrent respiratory depression due to naloxone's short duration of action relative to most opioids. Additionally, duration of action of opioids can be significantly increased in the setting of an overdose due to altered pharmacokinetics from enzymatic saturation [44]. A through history and physical exam should be performed to identify the causal agent. All transdermal applications should be removed and activated charcoal considered for oral ingestions within the previous hour [44].

Patients who overdosed on short-acting opioids should be monitored closely for at least 4–6 h and potentially discharged after this time frame if they no longer show feature concerning for opioid overdose. Patients who overdosed on long-acting opioids will need to be placed on a naloxone infusion and transferred to an intensive-care unit [44]. The recommended starting infusion rate is 2/3 of that required for initial reversal of respiratory depression per hour [45].

34.4.5 Aspiration Pneumonitis and Pneumonia

Aspiration events such as pneumonitis and pneumonia are the most frequent indications for ICU admission after opioid overdose. About a quarter of patients treated with naloxone went on to have aspiration pneumonitis or pneumonia based on a recently published, large retrospective, cross-sectional study. Patients using multiple substances are at greatest risk as they may develop vomiting from opioid withdrawal from naloxone while still having impaired airway reflexes from other substance use. However, this study showed that only about 3.7% of patients with pulmonary complications had episodes of emesis after administration of naloxone suggesting a majority of aspiration occurs prior to patients receiving medical attention. The study also showed that higher doses of naloxone were correlated with higher risk of pulmonary complications [46]. It is unclear if this is due to patients requiring higher naloxone had a more severe level of intoxication or an inherent causal property of naloxone.

34.4.6 Pulmonary Edema

Pulmonary edema has long been associated with naloxone with incidence estimated to be about 1.1%. Two proposed mechanisms of action are negative pressure pulmonary edema from inspiration against a closed glottis and due to increased permeability from a catecholamine surge in patients who develop opioid withdrawal [46]. However, no study has been able to establish a causal relationship. The aforementioned cross-sectional study suggested that higher doses of naloxone had a higher odds ratio of developing pulmonary edema. However, the study was not able to show statistical significance partly due to the low incidence of this complication. It is unclear if there is a confounding factor implicated in these results as other studies have demonstrated that pulmonary edema also occurs in patients with opioid overdose who never received naloxone [44, 46].

34.5 Assessment of Opioid Use Disorder while Inpatient

34.5.1 Comprehensive Assessment

A comprehensive assessment should be conducted in patients with opioid misuse or opioid use disorder. These patients are likely to have co-occurring medical conditions, psychiatric disorders, and other substance use disorders. Often these individuals are not receiving treatment for both medical and psychiatric comorbidities and are at higher risk for poor outcomes [47].

The medical history should include routine screening for medical conditions with particular attention to hepatitis, HIV, TB, trauma, and IV drug use and related infections [10–13]. The substance use history should include amount and frequency of current substance use, current treatment, and prior treatments or pharmacotherapies. Patients not already in treatment should be assessed for interest in initiating treatment and offered MOUD while inpatient. A psychosocial assessment can inform what barriers exist to accessing treatment and additional supports offered prior to discharge from the inpatient setting [10].

A thorough pain assessment and history of previous regimens is critical when initiating an inpatient pain regimen. Communication with outpatient pain physicians and review of the Prescription Drug Monitoring Program (PDMP) is helpful in seeing recent controlled substance prescriptions and assessing for any potential misuse. Methadone and buprenorphine prescriptions are not seen in the PDMP and outpatient providers and clinics must be contacted to confirm recent dosing.

34.5.2 Physical Exam

A routine physical examination should be completed on initial presentation and repeated in settings where there is concern for substance use while inpatient. The examination should include assessment for acute intoxication or withdrawal from other substances seen in Table 34.4 [10–13]. Special attention should be

Table 34.4 Common signs of intoxication and withdrawal from other substances [10–13]

Substance	Intoxication signs	Withdrawal signs
Alcohol	• Slurred speech • Ataxia • Decreased respiratory rate • Lower level of consciousness • Nausea and vomiting	• Seizures • Diaphoresis • Tremor • Irritability • Anxiety • Restlessness • Disorientation • Autonomic hyperactivity (tachycardia, hypertension, hyperthermia)
Benzodiazepines	• Sedation • Miosis • Slurred speech • Staggering gait • Decreased respiratory rate	• Seizures • Diaphoresis • Tremor • Irritability • Anxiety • Restlessness • Disorientation • Autonomic hyperactivity (tachycardia, hypertension, hyperthermia)
Stimulants (cocaine, amphetamines, methamphetamines)	• Euphoria • Restlessness • Mydriasis • Anorexia • Insomnia • Autonomic hyperactivity (tachycardia, hypertension, hyperthermia)	• Dysphoria • Irritability • Increased appetite • Prolonged sleep
Hallucinogens (phencyclidine (PCP), lysergic acid diethylamide (LSD) etc.)	• Nystagmus • Agitation • Perceptual distortion (visual, auditory) and hallucinations • Autonomic hyperactivity (tachycardia, hypertension, hyperthermia)	• No acute withdrawal syndrome
Cannabis	• Euphoria • Conjunctival injection • Autonomic dysfunction (tachycardia, hypertension, orthostatic hypotension) • Temporary bronchodilatation	• Irritability • Anxiety • Sleep disturbance

given to current or historical signs of IV drug use. New or old puncture marks may be seen at common injection sites such as the cubital fossa and the forearm [10].

34.5.3 Laboratory Tests

Initial lab testing should include hepatitis serology, HIV with patient's consent, a complete blood count and liver function tests to assess for infection or liver dysfunction [10]. If clinically indicated, testing for tuberculosis and sexually transmitted infections can be completed. Pregnancy testing should be completed in all women of reproductive age. A baseline electrocardiogram is helpful in assessing for cardiac conditions and QT prolongation as medications for treatment of opioid use disorder can cause QT prolongation. The clinician's assessment and judgment of each patient case can guide further testing.

34.5.4 Assessment for Substance Use Disorders

Evidence-based screening tools for substance use disorders should be part of the comprehensive assessment. The Substance Abuse and Mental Health Services Administration (SAMHSA) has multiple tools accessible to clinicians [48]. CAGE-AID is a brief four-question screening tool for substance use disorders [49]. Other screening tools include the Opioid Risk Tool and Screening, Brief Intervention, and Referral to Treatment (SBIRT). If a patient screens positive, then the inpatient treatment team should involve psychiatric and addiction specialists during the patient's hospitalization to provide further interventions and assure outpatient follow-up prior to discharge.

34.5.5 Risk Factors for Opioid Use Disorder and Opioid Overdose

Risk factors to developing OUD include comorbid substance use or psychiatric disorders, suicidal history, prior opioid overdose, long-term opioid therapy and higher daily dosing. Patients are at higher risk for overdose if they are on opioid doses greater than 90-mg morphine equivalents daily and longer-acting opioids, such as methadone and extended-release oxycodone. Concomitant use of alcohol and sedatives such as benzodiazepines and baseline respiratory disease also increase risk of overdose [47, 50]. Prior suicide attempts and intentional or unintentional overdoses are associated with greater risk of overdose [50–53]. A thorough initial

evaluation and history is important for identifying these risk factors and guiding further management. Various risk factors for opioid overdose and developing OUD are discussed in another chapter.

34.5.6 Assessment for Comorbid Psychiatric Disorders

Comprehensive psychiatric assessment is needed in individuals with OUD. Individuals with OUD and opioid misuse are more likely to have co-occurring psychiatric disorders such as depression, anxiety, PTSD, personality disorder, and other substance use disorders [3]. Suicide risk is 16 times greater in those with OUD than that of the general population [53]. Amongst this population about half receive treatment for co-occurring psychiatric and substance use disorders [3]. Psychiatric specialists can initiate treatment for these patients while inpatient including psychopharmacotherapy and psychosocial interventions such as cognitive behavioral therapy (CBT), motivational interviewing (MI), and contingency management (CM) [10–13]. Psychiatric evaluation can also be helpful in distinguishing primary psychiatric disorders from acute symptoms of dysphoria, anxiety, irritability, and sleep difficulty related to substance withdrawal or intoxication.

34.5.7 Inventory of Patient and Visitor Belongings

Individuals may continue to use substances while hospitalized. This can put them at risk for poor outcomes while inpatient [10, 54]. On initial admission, each patient should have a comprehensive evaluation and part of the substance use assessment should include inquiry of possession of substances or drug paraphernalia. Inventory of the patient or visitor belongings should only be done with the individual's consent. Individuals presenting to psychiatric settings must comply with full inventory checks and have limitations to certain belongings that may pose risk of harm to self or others and elopement.

In cases where there is concern for substance use while inpatient, a thorough physical examination should first be carried out and assure medical stability in the patient. Assessment should include differentiation between other substance intoxication presentations and potential medical risks [10]. These can be reviewed in Tables 34.1 and 34.4. Future withdrawal presentations should be foreseen and treated.

A patient may not be in agreement with a search of their belongings during a medical hospitalization. Starting the patient on a safety watch can mitigate the risks with ongoing substance use, and those declining a search of their belongings. Visitor restrictions may be needed for those who continue to present to the hospital despite requests to leave and there is ongoing concern for substance possession. Confiscation of substances should be handled as detailed in each hospital policy. The patient is

protected under confidentiality rights. Reassurance should be given to the patient that the goal of intervening on substance use is not for punitive or for legal reasons, rather it is for their safety and medical stability.

34.5.8 Urine Toxicology and Drug Testing

Drug testing has become a routine tool for pain physicians to assess patient compliance and comorbid substance use. Common testing samples include blood, urine, hair, saliva, sweat, and nails. Urine has become the most widely used due to its convenience of collection [55]. Until recently, standard practice was sequential testing with an initial screening immunoassay followed by confirmatory liquid or gas chromatography-mass spectroscopy testing [55].

More recently, there has been a shift towards doing a single-step chromatography-mass spectroscopy testing to reduce false-positives from immunoassay cross-reactivity and false-negatives as chromatography-mass spectroscopy methods have lower detection thresholds [56]. Additionally, this approach decreases turnaround time until final diagnostic results are obtained and cost by elimination of the initial screening immunoassay. This approach has been shown to potentially be effective in large academic centers that have the volume to establish an in-hospital chromatography-mass spectroscopy testing laboratory [56].

34.5.9 Immunoassay Testing and Gas Chromatography-Mass Spectroscopy

Immunoassay testing involves selective targeting via binding of antibodies. The three main types are enzyme-multiplied immunoassays, enzyme-linked immunosorbent assays, and fluorescence polarization assays. These techniques can be performed as point-of-care (POC) or laboratory testing. Turnaround time is usually less than 10 min for POC testing [57] and less than 60 min for laboratory-based testing [58]. The major limitation with these tests is the risk of cross-reactivity. Immunoassays target a specific substrate or component of the desired drug. Unfortunately, this can lead to false-positive detection of similarly structured compounds. Thus all immunoassay results need to be confirmed with diagnostic chromatography-mass spectroscopy testing.

Gas chromatography-mass spectroscopy allows quantitative analysis for specific molecular structure minimizing the risk of false-positives. However, this form of testing is more time-consuming, expensive, and requires specialized laboratory testing to perform [55]. Another similar testing method, liquid chromatography-tandem mass spectroscopy [56] has been used at some institutions as it may be more time-efficient [55].

34.5.10 Test of Choice in Inpatients

The test appropriate in each clinical scenario depends on the required turnaround time. POC immunoassays are used to in the emergency department when managing an unstable, acutely intoxicated patient [57, 58]. Similarly, the direct-to-diagnostic approach without sequential testing has been used in the outpatient chronic patient setting. This method requires several days before any results are obtained [56]. Inpatient pain medicine providers will encounter scenarios traversing both ends of this spectrum and will need to use clinical judgment to decide which test to order (Table 34.5).

34.5.11 Compounds to Test and Choice of Panel

Standard drug panels typically test for amphetamines, cocaine, marijuana, phencyclidine, benzodiazepine, and opiates. Opiates are opioids derived from poppy seeds. The two commonly used opiates in clinical practice are codeine and morphine. Pain providers should add additional opioid-specific panels assessing for various synthetic and semisynthetic opioids and their metabolites [55, 56]. Figure 34.1 shows the metabolic pathways for common opioids that will direct choice of panel and interpretation of results. Using panels that incorporate metabolites as well as primary drugs can reduce risk of false-negatives and help identify adulterated samples.

34.5.12 Urine Sample Adulteration

Patients attempt various techniques to falsify urine toxicology results. Commonly used techniques include urine dilution, substitution with another individual's urine, addition of household substances, addition of commercially available masking

Table 34.5 Important parameters in urine toxicology testing [55]

Test property	Definition
Cutoff level	Establishes the level at which a particular test will be considered a positive result for the test. Providers need to determine the ideal limit depending on risks associated with false-positives and false-negatives. Drug testing in the workforce uses a high cutoff to minimize false-positives. In clinical practice, a lower cutoff is often used to reduce false-negatives when assessing for patient medication compliance
Detection times	Time after last use that a substance remains detectable in the sample. This depends on numerous factors including cutoff levels, drug pharmacokinetics, dosage used, chronicity of drug use, patient body mass, urine concentration, renal function, and hepatic function. Common drug detection times are shown in Table 34.6

Table 34.6 Detection times of commonly used opioids [55]

Substance	Length of detection (days)
Morphine	2–3
Hydromorphone	2–4
Methadone	3
Oxycodone	2–4

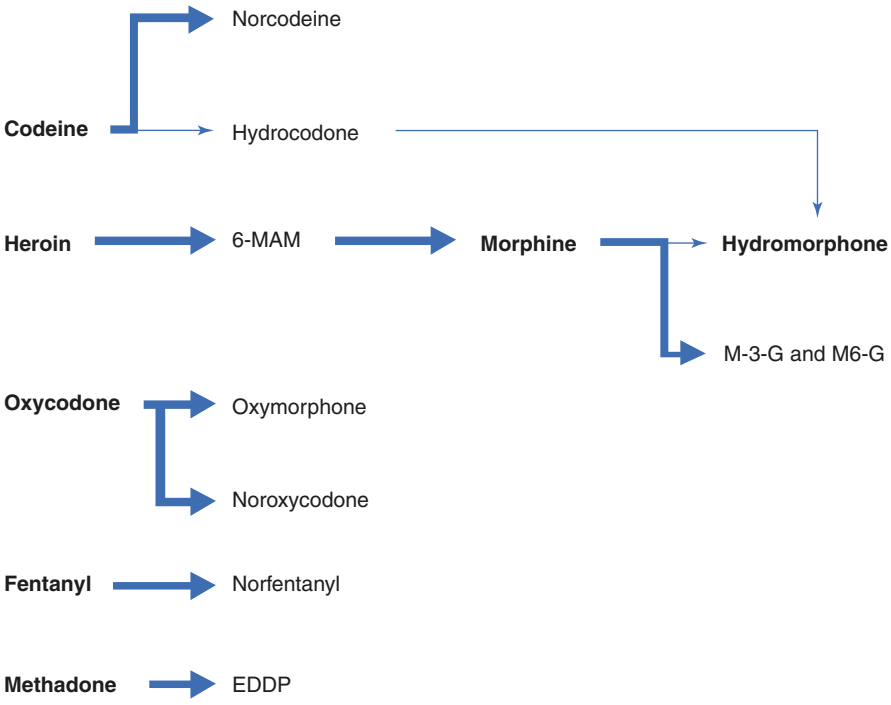

Fig. 34.1 Metabolic pathways for commonly used opioids [55, 56]

agents, and addition of medication directly into urine sample. Physical properties of sample, such as temperature, pH, and specific gravity, can be measured to assess sample validity [55]. Additionally, a thorough understanding of drug metabolism pathways can help with interpreting results.

Table 34.7 shows several commonly encountered urine toxicology examples. One more unique example is a patient prescribed Suboxone presenting with a sample positive for both buprenorphine and naloxone. When ingested orally as prescribed, naloxone is metabolized by first-pass metabolism and should not be identified in urine. This is likely either simulated compliance from adding Suboxone directly [56] to urine sample or attempted intravenous abuse of Suboxone. As with all diagnostic tests, urine toxicology results should be interpreted in the clinical context.

Table 34.7 Commonly encountered urine toxicology results and clinical interpretation

Example	Morphine	M3G and M6G	Hydromorphone	Clinical interpretation
1	+	+	+	Compliant
2	–	+	–	Compliant—M3G and M6G are not available as isolated compounds and are likely products of morphine metabolism [56]
3	–	–	+	Consider morphine diversion and hydromorphone abuse—Hydromorphone is also available in isolated form and a known drug of abuse [56]
4	+	–	–	Consider simulated compliance—Without metabolites one must consider possibility that urine sample was adulterated with medication after collection

34.6 Inpatient Management

34.6.1 Risk Reduction Methods

Risk reduction strategies are increasingly being employed worldwide to combat the opioid epidemic. At the community level, Supervised Injection Facilities (SIF) have demonstrated significant public health benefits. The first SIF was opened in Switzerland in 1986. Since that time, SIFs have been developed throughout Europe [59]. The first government-sanctioned SIF in North America was established in Vancouver, British Columbia, Canada [59, 60] there have never been any government-supported SIFs in the United States, multiple clandestine SIFS have functioned since 2014. Research has shown the SIFs reduce opioid overdoses, decrease public injections, decrease publicly discarded needles, and facilitate referral to OUD treatment without increasing overall drug-use or drug-related crimes in the surrounding areas. Despite these successes, operating SIFs has remained a controversial issue.

Currently most hospitals operate under an abstinence-based policy. This policy places people with substance use (PWSU) at significant health risks. At baseline PWSU often have poor health in part due to prevalence of blood-borne infections such as HIV and have high rates of inpatient admissions. According to a prospective cohort study that followed patients for 3 years, 35% of PWSU were hospitalized at least once and 20% were hospitalized multiple times. The two most common reasons for admission were pneumonia and soft-tissue infection [61].

Due to the hospital-abstinence policies, PWSU often turn to high-risk drug practices such as needle sharing and injecting alone [62]. According to one study, 44% of PSWUD who have been admitted to a hospital report to have actively used illicit drugs while admitted [63]. The inability to access illicit drugs, also leads to high

rates of discharge against medical advice, which is estimated to occur in about 30% of admitted injection drug users [62]. This leads to inappropriate medical care and frequent readmissions.

There has been increasing interest in offering a SIF for inpatients. One study whose primary outcome was to assess PSWUD willingness to participate if admitted to the hospital showed that about two-thirds of PWSU would participate. About 90% of patients who had left a hospital AMA in the past and about 75% of patients who had used illicit drugs while admitted to a hospital reported they would be interested if offered. The most common reason for PWSU interest in the SIF was that it would allow them to stay in the hospital for their medical care. This study was performed in Vancouver, Canada which already has a functioning outpatient SIF [62]. All three studies that have addressed this same question in the United States have concluded that PWSU would be interested in using inpatient SIFs [63].

There continues to be significant resistance to establishing such practices beyond the legal limitations. Opponents advocate that funds would be better allocated to provide these patients with preventative and treatment services [59, 60]. However, SIF facilities provide an opportunity to engage and educate PWSU about treatment and therapy options. Estimates vary widely, with 10–42% of outpatient SIF users entering an addiction treatment program [59–64].

34.6.2 Initiating OUD Treatment While Inpatient

Initiating treatment for substance use disorders in the acute hospital setting is feasible and effective [5–9] and results in better medical and substance use disorder outcomes including decreased emergency visits, increased completion of medical treatment, and transition to outpatient substance use treatment [6, 8]. Without substance use treatment, the majority of individuals will return to substance use upon discharge from an inpatient setting and are at high risk for poor outcomes particularly for opioid use disorder and overdose [14, 15]. Engaging patients in treatment for opioid use disorder improves outcomes for some of the highest risk individuals [7].

Currently there are three FDA-approved medications for OUD: methadone, buprenorphine, and extended-release injectable naltrexone. All patients with OUD not on pharmacologic management should be recommended one of these treatment options and connected with outpatient substance use treatment [10–13]. The choice of treatment should be a shared decision between the clinician and patient. Inpatient psychiatric and substance use disorder specialists can assist in this process with consideration of the patient's preference, previous treatment, and setting of treatment (supervised opioid treatment program versus outpatient office setting for buprenorphine or naltrexone). Patients declining pharmacotherapy for OUD should be provided with outpatient referrals for substance use treatment and an intranasal naloxone kit upon discharge.

Although all effective treatments, there are specific considerations and limitations in the inpatient setting surrounding each OUD medication.

34.6.3 Opioid Agonists

Both methadone and buprenorphine can be used to treat pain and as MOUD. Buprenorphine is different than methadone in that it can precipitate opioid withdrawal given its higher affinity for the mu-opioid receptors than other opioids. Opioid-tolerant patients will need to enter a state of mild to moderate opioid withdrawal or a COWS score greater than 10 prior to initiating buprenorphine [34]. Generally initiation of buprenorphine is at least 6–12 h after last use of short-acting opioids or 24–72 h after last dose of long-acting opioids [10]. It is important to symptomatically manage opioid withdrawal as subjective pain might increase and untreated withdrawal symptoms will limit comfort in transition to buprenorphine. Specific considerations in initiating methadone or buprenorphine are similar to principles discussed in the section "Medications in Opioid Withdrawal."

34.6.4 Extended-Release Injectable Naltrexone

Extended-release injectable naltrexone in the inpatient setting is limited to those whose pain is managed with non-opioid analgesics and individuals not on opioids for 7–14 days. There are current studies looking at more rapid induction methods although not yet widely practiced [65]. This timeline is often a barrier to initiating extended-release injectable naltrexone, and it is not widely available on hospital formularies. For those who have been off opioids for this timeline, an oral naloxone challenge can be useful before initiating naltrexone treatment. A dose of 0.4–0.8 mg of naloxone is administered and the patient is observed for precipitated withdrawal [10]. Careful consideration should be given to those interested in outpatient follow-up for extended-release injectable naltrexone as individuals will need to abstain from opioid use for an extended period of time and are at high risk for relapse and overdose.

34.6.5 Naloxone Kit and Outpatient OUD Treatment on Discharge

All patients discharged on daily opioid dosing greater than 90-mg morphine equivalents, those on longer-acting opioids (methadone or extended-release oxycodone), and those with a history of OUD or substance misuse should be discharged with an intranasal naloxone kit [66]. Patients at high risk for opioid overdose and those with

OUD also need early follow-up with substance use treatment. Substance use treatment includes MOUD, counseling and other supportive services, and is offered by treatment programs or providers in the outpatient setting. It is encouraged to involve family members and significant others in education and training in naloxone administration prior to discharge.

34.7 Managing Pain in Inpatients Continuing to Use Outside Drugs

PWSU are at increased risk for presenting to the emergency department or be admitted for management of pain. Lacerations, physical assault, fracture, abdominal pain, and musculoskeletal problems are among the ten most common reasons PWUD present to the emergency department. Fractures, lacerations, trauma, osteomyelitis, and pyelonephritis are all common reasons PWUD get admitted to the hospital [61]. In addition, many of these patients will require surgical intervention for various reasons including treating the conditions mentioned above.

As mentioned earlier, fear of not having pain adequately treated is one of the main reasons PWUD continue to use illicit drugs while admitted. The most important step in managing pain in these patients is to open a dialogue with the patients to answer questions and assuage their concerns. The patient needs to understand that their pain will be taken seriously and addressed by the pain management provider and primary team. The pain management provider should also discuss the risks associated with the patient concurrently using outside substances. Patients using outside illicit opioids while also being treated with inpatient prescribed opioids increases risk of overdose and makes it difficult for providers to assess opioid requirements leading to even worse analgesia. In cases where prevention-based approach to using outside substances has failed, providers should focus on a multimodal plan to minimize opioids and choose opioids with lowest risk of overdose.

Regional anesthetic techniques can be used to target the source of pain. All patients without contraindications should be prescribed NSAIDs and acetaminophen. Other non-opioid pharmacologic options include ketamine and lidocaine infusions. Both of these drugs can be administered safely in unmonitored settings. Although ketamine is not a respiratory depressant, airway reflexes will be impaired in a dose-dependent fashion. These risks need to be considered in the context of the patient's primary pathology. Patients receiving lidocaine infusions need to be monitored closely for signs of local-anesthetic systemic toxicity. Multimodal analgesia in the context of opioid-tolerant individuals is discussed in detail in another chapter. When opioid-based analgesia is required, short-acting opioids should be used to minimize the risk of overdose. Patient-controlled analgesia are ideal options as the patient will be able to titrate medications to desired effect.

34.8 Summary

- Identifying and managing patients with OUD remains a complex issue for inpatient medical providers.
- Patients with OUD have increased incidence of hospital admission and are at risk for poor medical outcomes [4].
- It is estimated that up to 44% of illicit drug users may actively continue to use substances while admitted [63]. Unidentified and untreated substance use carries risks of overdose, withdrawal, and is linked to patients leaving against medical advice. Managing acute opioid withdrawal using clinical assessment tools and medications, such as opioid and alpha-2 agonists, can decrease discomfort and risk of patients leaving against medical advice.
- All admitted patients should be screened for SUD with a comprehensive history and physical examination.
- Further testing with urine toxicology may be considered on a case-by-case basis for both diagnostic or monitoring purposes. Currently, only 20% of all patients with OUD are on appropriate MOUD therapy [67].
- The inpatient admission is an ideal opportunity to start patients on MOUD and establish appropriate [67] outpatient follow-up.
- New rapid-induction protocols that allow initiation of therapy while inpatient are becoming more established for buprenorphine and naltrexone [10].
- Methadone can also be started as an inpatient but is often limited by outpatient access to a federally certified opioid treatment program.
- Early identification and management of OUD and other SUDs during acute hospitalization improves medical outcomes and reduces overdose deaths.

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Chapter 35
Considerations in Pediatric Inpatients

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35.1 Introduction

Pain in inpatients, specifically hospitalized children, is common, under-recognized, and undertreated [1]. Pain in patients, not specifically children, has been shown to be associated with high rates of functional impairment, healthcare utilization and associated costs [2]. Studies, outside of the United States, have shown that as many as 33% of pediatric inpatients experience moderate to severe pain, with 88% of these cases being characterized as acute and the remaining 12% characterized as chronic [3]. Chronic pain has been associated with greater odds of using other specialty care, complementary and alternative medicine, and emergency care [4]. Many children endure unacceptable levels of pain during hospitalization, with around 49% of subjects reporting clinically significant levels of worst pain, and 21% of subjects reporting clinically significant levels of usual pain [5].

The knowledge of the prevalence and sources of pain in pediatric inpatients is limited. Furthermore, it is unclear whether pain management in pediatric inpatients has improved over the years, with proposals for more aggressive pain prevention and management, and improvements in analgesic prescription and administration practices and non-pharmacological pain control methods [5]. Better management of pediatric pain is important to healthcare systems, particularly to reduce emergency department use. In this chapter, we review the pathophysiology, risk factors, differential diagnosis, treatment, and assessment tools used related to pain in pediatric inpatients. We also review common approaches as well as challenges related to managing pain in pediatric inpatients.

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35.2 Pathophysiology

The underlying pathophysiology of pain in pediatric inpatients includes acute nociceptive pain, neuropathic pain, psychological-social-spiritual-emotional pain, total pain, and chronic persistent pain [6]. Nociceptive pain refers to somatic or visceral pain that arises from the activation of peripheral nerve endings, and neuropathic pain refers to pain that results from injury or dysfunction of the somatosensory nerves [6]. Psychological, social, spiritual, and emotional pain are all terms used to describe mental pain and suffering. As the name implies, total pain refers to all a person's physical, psychological, social, spiritual, and practical struggles. Chronic persistent pain is used to describe pain that extends beyond the expected time of healing. Pain in pediatric inpatients commonly originates from some combination of pathophysiology [6]. Needle pokes for intravenous access or laboratory investigation commonly represent the worst pain experience for pediatric inpatients, as well as pain associated with surgeries or procedures [7].

35.3 Risk Factors

One study surveyed pain predictors in an inpatient pediatric population in a teaching hospital, and determined that gender was a prominent risk factor, as pain has been significantly associated with females [8]. Increased pain prevalence has also been associated with young adults or divorced/separated individuals, as well as patients during extended hospitalizations [8]. However, some studies have also shown that pain intensity is not necessarily significantly related to age, gender, patient type (medical, surgical), or diagnostic category [5]. Other known risk factors for pediatric pain include previous history of chronic pain, positive family history of pain, comorbidities(including depression, anxiety, insomnia, fatigue), and psychosocial and environmental stressors.

35.4 Diagnosis

Epidemiological studies of pain in pediatric inpatients have reported variable causes of pain including pain due to disease, surgery, and intravenous lines [5]. The common causes of pain presentations in pediatric inpatients includes postoperative pain (e.g. needle injections, etc.), cancer pain stemming from either the malignancy itself or as a result of the cancer treatment, sickle cell disease, and episodes of inconsolability due to medication side effects or inappropriate pain and sedation medication [6]. The differential diagnosis of inpatient pain should also include migraines, intractable headaches, complex regional pain syndrome, conversion disorder or functional neurological disorder, burn wounds, and even-

dental pain [9]. Pediatric chronic muscular pain also has a broad differential diagnosis that should be considered when appropriate [10]. Meaningful assessment and investigation of pain is important for accurately identifying the underlying cause of pain given its major impact on physical, emotional, and cognitive function, on social and family life, and on the ability to work and secure an income.

A comprehensive investigation of any pain condition requires documenting pain history, physical examination, and specific diagnostic tests. A general medical history is an important part of the pain history as it can reveal important aspects of co-morbidities contributing to a complex pain condition, and must clarify location, intensity, pain descriptors, temporal aspects, and possible pathophysiological and etiological issues [11, 12]. Physical examination includes general physical examination, specific pain evaluation, neurological examination, musculoskeletal system examination, and assessment of psychological factors [11, 12].

35.5 Treatment

Treatment of pain in pediatric inpatients now consists of multimodal analgesia or some improved combination of non-pharmacological interventions, pharmacological interventions, and other modalities [6, 13]. Multimodal analgesia refers to the use of analgesics and adjuvants, procedural interventions, physical rehabilitation, psychological and integrative therapies that act synergistically for more effective pain control and potentially fewer side effects than any one intervention, even without requiring the use of opioids [6, 13]. Multimodal approaches are based on the belief that pain depends on the patient's entire clinical picture and perception of the experience pain, and should be treated as such [6]. Analgesia may include basic, traditional analgesics (e.g. paracetamol/acetaminophen and ibuprofen); opioids (e.g. morphine, fentanyl, hydromorphone, oxycodone or methadone); and adjuvant analgesics including gabapentinoids, α-agonists, low-dose tricyclics, NMDA channel blockers and nerve blocks or neuraxial anesthesia [6]. However, given how pain is increased by a myriad of factors including home and school stressors, anxiety, depression, and sleep hygiene, pharmacology alone can be insufficient to treat pain in pediatric inpatients [6]. In fact, one study reported that non-pharmacologic modalities were rated by patients as more effective than pain medications [7]. Therefore, multimodal treatment may also use physical therapy and exercise, especially for physically deconditioned patients, psychotherapy, proper sleep hygiene techniques, stabilizing life at school and home to normalize function and treat and reduce pain.

Recent studies have explored less traditional, non-pharmacological approaches that can be integrated into pain treatment, and include breathing strategies, aromatherapy, biofeedback, progressive muscle relaxation, autogenic training, mindfulness, yoga, and self-hypnosis [14]. Acupuncture has also been explored for acute and chronic pediatric pain [15, 16]. Current studies are underway to explore the

impact of integrative pediatric care on pain outcomes [17, 18]. Newer technology-based methods such as virtual reality are also being explored [19], and have shown some benefit in decreasing pain ratings in pediatric burn patients [20].

In cases of chronic pain and no clinical signs of tissue injury, opioids have been determined to not be beneficial [6]. Pediatric inpatients, especially those with severe pathologies, may experience chronic pain on top of underlying medical conditions, and thus require treatment for acute pain as well as chronic pain. Children with underling anxiety or depression are more likely to develop chronic pain compared to those without anxiety or depression [6, 21]. "Catastrophizing" is a personality trait among pediatric patients and their parents who can ruminate and obsess about the patient's pain symptoms. Thus, fear of pain [6, 22] and catastrophizing is a concern because these factors can prolong the duration and severity of pain experienced [6, 23], and require the involvement of a family therapist and social worker who are exclusively working with the parents to talk about parenting strategies about how to reduce parental catastrophizing and restore the function of the patient [6, 14].

The use of different multimodal analgesia techniques varies with the specific age range of pediatric inpatients. For instance, treatments such as physical therapy will vary in regimen for adolescents compared to toddlers, and treatments such as biofeedback are more suited for older children. Thus, multimodal analgesia needs be flexible and adaptable according to the activity and cognitive level of the pediatric patient, and appropriate for the age group. Treatment intervention instructions may need to be provided to the patients and/or the parents, depending on the age of the patient and the ability to implement interventions [6]. Furthermore, the pharmacodynamics and pharmacokinetics of analgesic medication is altered in infants younger than 3–6 months who metabolize medications differently than older children. As a result, the younger the patient, for instance, the lower the starting dose for opioids are for treating acute pain. However, infant patients more rapidly develop tolerance, which means that they very quickly get tolerant to opioids and require a more rapid dosage titration compared with older children [6].

Overall, treatment of pain in pediatric inpatients has become less dependent on opioids as the only therapy and much more reliant on a multimodal approach involving physical therapy, psychotherapy, stabilizing life stressors, normalizing life activities, and arriving at a personalized regimen of analgesic medications [6]. Opioids are not indicated for primary pain disorders and along with other medications, are usually not first-line therapy [14]. Short-term opioids continue to be involved in acute pain management, but multimodal, opioid-sparing analgesia is preferred for long-term pain control [6]. In fact, the only patients on long-term opioids anymore are those with recurrent tissue injury, such as children with epidermolysis bullosa or osteogenesis imperfecta, or those during their end-of-life period, and treatment of pediatric inpatients with sickle cell disease or avascular necrosis no longer involves long-term opioids [6].

35.6 Pain Assessment Tools

Valid and reliable assessment of pain is essential for both effective pain management and clinical and translational research, but pain assessment continues to be a challenge especially as it has been objectively hard to measure. Numerous instruments have been developed for different types and subtypes of pain conditions in order to assess qualitative aspects of pain and its impact on function [11]. Assessment of pain must consider other factors such as intellectual disability or developmental delay. Pain assessment is complicated by several other bodily and mental symptoms such as fatigue, depression, and anxiety, all affecting quality of life.

Pain has commonly been assessed with one-dimensional tools such as numeric rating scales (NRS) or visual analogue scales (VAS), as well as a four-point verbal categorical rating scale (VRS), which primarily serve to quantify the patient's subjective feeling of present pain intensity. The VAS and NRS have been shown to be generally in agreement and equally sensitive in assessing acute pain after surgery and superior to the VRS in general [11, 24]. An NRS with numbers from 0 (indicating no pain) to 10 (indicating worst pain imaginable) is more practical than a VAS, easier to understand for most people, and does not require clear vision, dexterity, paper, and pen. With the NRS, one can determine the intensity of pain even remotely using telephone interview or recording of NRS data by the patient directly into the database of a computer [11, 25]. For younger children (ages 3 years and up), pain scales with happy and unhappy faces are well validated—one such example is the faces pain scale [11, 24].

Since pain has a major impact on physical, emotional, and cognitive function, social and family life, and on the ability to work and secure an income, meaningful assessment of pain, whether acute or chronic, is essential to monitoring treatment effects. A comprehensive assessment of any pain condition requires documenting pain history, physical examination, and specific diagnostic tests. A general medical history is an important part of the pain history, often revealing important aspects of co-morbidities contributing to a complex pain condition. The specific pain history must clarify location, intensity at rest and during motion, pain descriptors, temporal aspects, and possible pathophysiological and etiological issues. Physical examination includes general physical examination, specific pain evaluation, neurological examination, musculoskeletal system examination, and assessment of psychological factors [11, 12].

Other forms of assessment include quantitative sensory testing (QST) with specific and well-defined sensory stimuli for pain thresholds and pain tolerance [11, 26, 27]; low-cost sensory testing: cold water in a glass tube (for cold allodynia—Aδ- and C-fibers), one glass tube with about 40 °C warm water (for heat allodynia—C-fibers), cotton wool and artist's brush for dynamic mechanical allodynia, and a blunt needle for hyperalgesia and temporal summation of pain stimuli [11]; diagnostic nerve blocks [11, 28, 29]; pharmacological tests [30]; and conventional radiography, computerized tomography, magnetic resonance imaging [11].

Chronic pain, given its impact on physical, emotional, and social functions, requires assessment involving multidimensional qualitative tools and health-related quality of life instruments. There are a number of pain assessment instruments constructed for evaluation of pain-related functional disturbances in specific diseases or pain conditions including the Western Ontario and Macmaster Universities osteoarthritis index; the arthritis impact measurement scale; rheumatoid arthritis pain scale; disability of arm, shoulder and hand; patient-specific functional scale—in which the patient is asked to list five activities or tasks that they regularly performed before the onset of pain, but now find difficult to perform [11]. However, these conditions are more frequently encountered in the adult population instead of pediatric inpatients. Other chronic pain assessment tools include the Brief Pain Inventory (BPI) which assesses pain severity and the degree of interference with function, using 0–10 NRS [31]. The McGill Pain Questionnaire (MPQ) and the short-form MPQ (SF-MPQ) evaluate sensory, affective–emotional, evaluative, and temporal aspects of the patient's pain condition [32]. The Massachusetts General Hospital Pain Center's Pain Assessment Form is another brief patient self-report form covering the essential issues needed in a self-report pain form [33]. The self-complete Leeds Assessment of Neuropathic Symptoms and Signs [34] and the neuropathic pain scale [35].

The COMFORT scale for pediatrics measures distress in unconscious and mechanically ventilated infants, children, and adolescents. It relies on nine parameters: alertness; calmness or agitation; respiratory distress; crying; physical movement; muscle tone; facial tension; arterial pressure; and heart rate. Each indicator is scored between 1 and 5 based upon the behaviors exhibited by the patient, who is observed unobtrusively for about 2 min. The sum of scores can range between 9 and 45. A score of 17–26 generally indicates adequate sedation and pain control [36]. The CRIES Pain Scale is another validated scale specifically for neonates ages 32 weeks of gestational age to 6 months. Each of five categories is scored from 0 to 2: crying; requires O2 for saturation below 95%; increased vital signs (arterial pressure and heart rate); expression—facial; and sleepless [37]. The FLACC Pain Assessment Tool is another tool used for non-verbal pediatric patients that incorporates five categories of pain behaviors: facial expression; leg movement; activity; cry; and consolability [38]. The Faces Pain Scale is a self-report measure used to assess the intensity of children's pain [39]. A summary of the approach for pediatric pain management is summarized in Table 35.1, and commonly used pain assessment tools are outlined in Table 35.2.

35.7 Challenges in Management of Pain While in the Hospital

There are still numerous challenges to management of pain in pediatric inpatients. Children in rural hospital settings may face unique challenges due to resource limitations in the rural setting [40]. One study that used semi-structured interviews of

Table 35.1 Approach to inpatient pediatric pain assessment and management

1. Conduct a thorough history and physical exam. This should include a detailed family and psychosocial history, including the patient's pain history as well as environmental stressors
2. Conduct a thorough review of other chronic disease states
3. Conduct a thorough review of the patient's past and current treatments. This should include both over-the-counter medications and complementary/alternative medicine treatments, as well as an understanding of which treatments/analgesics have been helpful, ineffectual, or harmful. Furthermore, any treatments that have been ineffectual or have caused adverse effects should be stopped or tapered
4. Identify the type of pain that the patient has (neuropathic, musculoskeletal, etc.), and review the evidence available regarding treatment of the type of pain the patient has (non-pharm, interventional, pharmacologic, etc.)
5. Review and discuss all possible and reasonable treatment options with the patient and the family, considering the patient's comorbidities, drug interactions, and preferences. Patients and the family should be educated about all adverse effects and expected efficacies, as well as scheduling of doses and titrations needed
6. In the inpatient setting, the patient's pain symptoms should be assessed daily using the age and condition appropriate operational and self-assessment scales, as well as the presence of any adverse effects. Medication doses and regimens should be adjusted accordingly
7. Discharge planning should include communications with the patient's local provider, pharmacy, and healthcare team. The patient should be given written and verbal instructions regarding how to take any analgesic regimen

Table 35.2 Commonly used pain assessment tools

Assessment scale	Age range	Cognitive status	Critical care	Verbal or non-verbal patients	Observational vs. self-assessment
COMFORT	Children from birth to 18 years of age	Intact or impaired	Recommended for critical care settings	Verbal and non-verbal patients	Observational
CRIES	Infants at least 38 weeks of gestation	Intact or impaired	All settings	Non-verbal	Observational
FLACC	2 months–7 years	Intact or impaired	Can be used in critical care settings	Non-verbal	Observational
Faces	Recommended for very young children, and 4 years and older	Intact	All settings	Verbal	Self-assessment
Numeric rating scales (NRS)	Children 8 years and older	Intact	All settings	Verbal	Self-assessment
Visual analogue scales (VAS)	Children 7 years and older	Intact	All settings	Verbal	Self-assessment
Verbal categorical rating scale (VRS)	Children 6 years and older	Intact	All settings	Verbal	Self-assessment

registered nurses (RNs) reported many challenges in rural settings. For instance, rural RNs needed to practice as generalists as they care for many types of patients. Resource challenges included a lack of specialist expertise and educational opportunities. Pediatric pain was not perceived as a priority within their organizations. Most participants perceived there were no explicit standards for pain care. There is a need for improvement of pediatric pain management, especially in areas where resources are scarce including rural settings [40].

Standardization of pain management is also a challenge, especially when specialist knowledge is not available. Retrospective studies of more than five million pediatric hospitalizations, have found wide variation across hospitals in opioid use and length of use even after adjusting for patient demographic and clinical characteristics, hospital type, and hospital patient volume [41]. Although this study cannot ascertain whether the observed use of opioids was appropriate, the substantial variations in exposure proportion and length of exposure across hospitals suggest that a significant opportunity exists to improve the use of opioids for pediatric inpatients. The same study found even greater hospital-level variations in opioid use and length of use for children who died during hospitalization. This study documents the variety of opioids used among pediatric inpatients, underscoring the importance of performing comparative effectiveness and safety studies to better inform the rational use of different opioids [41].

Pain management of certain conditions lacks studies and guidelines: for instance, inpatient management of pediatric status migraine and intractable headache is limited because of a lack of studies and guidelines [42]. Pain management in pediatric palliative care also faces unique challenges. Although pediatric pain management in palliative care has developed over the years, much of what is done in palliative care is based on anecdotal evidence or adult studies. Although advances in this field have been made, including publication of guidelines [43], significant gaps exist in terms of the evidence base, education and access to essential medications and both interdisciplinary and international collaboration are required to meet these gaps [43].

Most pediatric inpatients with common primary pain disorders experience an episode of pain, and just go on with their normal life and do not become dysfunctional [6, 44]. However, 4–5% of pediatric inpatients reportedly experience pain frequently and can become dysfunctional, characterized by short-term outcomes including absences at school and insomnia. Furthermore, psychosocial and environmental causes of pain (due to school, home and family life, etc.) can be challenging to address, thus making pain difficult to treat. Chronic pain in pediatric inpatients can be difficult for clinicians to manage, and many children and teenagers at one time or another experience prolonged pain [6, 45]. Despite increased focus on pediatric pain, uncontrolled pain is still a problem for hospitalized pediatric inpatients.

Documentation of pain beyond numerical representation continues to be a challenge. Diagnosis of pain can also be complicated given the multi-factorial nature of acute and chronic pain conditions. There continues to be a debate on whether the multidimensionality of pain narratives' composition is a desirable feature of documentation and how narratives can be refined and improved. There is potential for

further investigation into how health care professionals' pain narratives could have a role in generating guidelines for best pain documentation practice beyond numerical representations of pain intensity [46].

One recent survey identified barriers across pediatric hospitals including inadequate or insufficient physician medication orders, insufficient time allowed to premedicate before procedures, insufficient premedication orders before procedures, and low priority given to pain management by medical staff [47]. Quality improvement studies of patients receiving inpatient care showed that leaders of health care organizations need to provide the support and resources needed to incorporate established pain management guidelines and standards into institutional culture [48]. Transforming pediatric pain management to family-centered care also continues to be an abstract concept for providers that needs to be integrated more in inpatient pediatric care [49].

35.8 Management of Pain in the Inpatient Setting

Management of pain in pediatric inpatients can be complex since drug responses in children differ from adults due to age-related differences, there is a relative limited number of therapeutic options (specifically analgesic medications) given the limited number of conducted clinical trials in children, and assessment of efficacy and tolerance of medications can be complicated by the inability of pediatric patients to communicate properly [50]. Opioids such as tramadol and codeine may be used in addition to paracetamol and ibuprofen for moderate nociceptive pain in pediatric patients. Codeine prescription has been restricted in children in recent years because of the risk of fatal overdoses linked to the variable activity of cytochrome P450 (CYP) 2D6 [50]. While tramadol is a safer alternative compared to codeine, tramadol pharmacodynamic effects, efficacy, and safety, are also influenced by CYP2D6 activity. Consequently, tramadol requires a personalized approach with dose adaptation in children to be safely and effectively used [50]. In cases of moderate to severe nociceptive pain, morphine is an option [50]. However, current treatments have shifted towards opioid-sparing pharmacological approaches which utilize medications including intravenous parecoxib, inhaled methoxyflurane, and sublingual ketorolac or tramadol as well as the avoidance of codeine [51]. Ambulatory continuous peripheral nerve blocks can provide postoperative analgesia in pediatric inpatients and may reduce the need for inpatient parenteral opioid therapy [52].

Interdisciplinary, multimodal pain treatment in the pediatric inpatient setting can consist of individual and group cognitive behavioral, occupational, physical and recreational therapy, education and family intervention in addition to pharmacological treatment. Even over a two-week period, interdisciplinary pain management has been shown to result in short- and long-term improvements in multiple clinical parameters including pain intensity, physical functioning and internalization and mean number of medical visits, school absence and frequency of pain medication, as well as improvements in patient and parent-assessed satisfaction and pain experience [53].

Table 35.3 Questions to ask during inpatient pediatric pain management

1. What pain symptoms is the patient experiencing?
2. Has the patient's condition changed?
3. Has the patient experienced any adverse events?
4. Is the analgesic treatment still needed, and will the patient continue to benefit from treatment?
5. Have the pain management and treatment guidelines changed?
6. Is the pain treatment being used to treat an iatrogenic problem?
7. Would discontinuation of treatment cause problems?

Team coordination when planning for procedures is also important when it comes to management of pain in the inpatient setting. Minor procedures occur daily in all children's hospitals, yet team coordination when planning for these procedures is often overlooked, but interdisciplinary approaches have been developed and piloted [54]. The Look before You LEAPP™(Listen, Evaluate, Anticipate, Plan, and Proceed) program was developed by a group of interdisciplinary healthcare professionals to provide consistent care to all children undergoing inpatient procedures and support interdisciplinary teamwork and education [54].

Some clinically relevant questions that providers must ask themselves throughout inpatient pediatric pain management are listed in Table 35.3.

35.9 Discharge Plan for Pain Management

Before discharge, all pain medications administered to the patient and the patient's response should be documented. Care providers should determine if the patient is safe for discharge, which includes assessment of vital signs, cognitive status, physical condition, transportation, and counseling and education for the patient's family. Discharge treatment should include a consideration of prescription and over-the-counter medications, as well as non-pharmacological and multimodal therapies (exercise, stress/relaxation, and sleep hygiene) as discussed in this chapter [55].

Discharge plan for pain management includes advising the patient and the family to do the following: (1) follow instructions for prescription pain medications (narcotics, opioids, muscle relaxers, steroids, anesthetics, anti-anxiety medications, antidepressants, and anticonvulsants) and over-the-counter medications (nonsteroidal anti-inflammatory drugs, acetaminophen, and pain creams, gels, or patches. Advise patients how to watch and manage side effects (especially constipation). Patients should specifically be instructed to not suddenly stop taking any prescription pain medications or drink alcohol while using prescription medications, although the latter is less common in pediatric patients, (2) seek care immediately if patient has severe pain, and (3) follow-up with healthcare provider if patient has moderate to severe pain even after taking prescription medication, a new pain sensation that is different from pain experienced before, and if there are any other questions or concerns.

35.10 Summary

- Research supports the use of comprehensive, interdisciplinary and multimodal treatment approaches for pain management in pediatric inpatients. Inpatient pediatric pain management has changed to emphasize multimodal and multidisciplinary therapy, as well as traditional opioid-sparing pharmacological therapies [51].
- Non-pharmacologic therapies are effective in treating pediatric pain and should be a routine and integral part in managing pain in the inpatient setting [7].
- Inpatient pediatric acute pain services have expanded to include the use of advanced treatments such as nerve blocks and infusions of centrally acting pain modulators [51].
- Treating pediatric chronic pain should occur on an outpatient basis instead of in the inpatient setting, as chronic pain management in the outpatient setting has been further shown to lead to cost savings for the hospital [2].
- Studies point that there is still a need to improve in how pain is managed in pediatric inpatients despite advancements in treatment, and the existence of inpatient and outpatient pediatric pain consult teams [7].
- Improving pain management in pediatric inpatients leads to improved clinical outcomes and increased satisfaction of patient, families, and staff [7, 56].
- Optimal pain management carries important financial implications for our healthcare system because childhood pain brings significant direct and indirect costs from health care utilization and lost wages associated with time off from work due to caring for the pediatric patient [7, 55, 57]. Furthermore, patient and parent satisfaction scores will potentially have a future impact on reimbursement to children's hospitals [7].

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Chapter 36
Pain Management for Prisoners in the Inpatient Setting

Hemant Kalia, Neha Pawar, and Alaa Abd-Elsayed

36.1 Introduction

The United States has the world's highest rate of incarcerated population. Providers practicing outside of correctional facilities get little dedicated training and are unaware of guidelines for the treatment of inmates. The Eighth Amendment of the US Constitution grants basic health care for incarcerated individuals within or outside of dedicated correctional facilities.

It is found that incarcerated patients in the acute hospital setting are mostly young male. Federal Law, individual health care professional practices, physical restraint, discharge counseling, and surrogate decision-making are affected by a patient's incarcerated status. Incarcerated patients have protected right to health care but may experience exceptions to physical comfort, health privacy, and informed decision-making in the inpatient or acute care settings.

Most of the research on the management of issues associated with incarcerated patient in the inpatient settings is limited and primarily focuses on the care of pregnant women. It is vital that the clinicians and health care facilities should work toward creating evidence-based and legally supported guidelines for the care of incarcerated individuals in the inpatient setting [1].

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36.2 Types of Health Care outside Prisons

- **Off-site care:** Medical care provided outside of prison premises. It could be provided at a hospital, surgical center, or specialty clinic, such as for radiology or dialysis services.
- **Inpatient hospitalization:** An admission to a medical institution, such as a hospital, for longer than 24 h. This is the only type of care for which state Medicaid agencies may provide coverage for incarcerated individuals, if they are eligible and enrolled in the program.
- **Outpatient care:** Emergency, diagnostic, or therapeutic services that do not require the patient to be admitted to a hospital.

Some corrections facilities and private contractors are willing to pay this fee, especially if the hospital has a contract with them Telemedicine and mobile services may help to reduce inpatient stays and costs as the providers may be able to diagnose the illness and prevent a trip to the hospitals [2].

36.3 General Guidelines for Medical Staff in Providing Care for Detainees

1. Complete a thorough History and Physical Examination.
2. Care provided or needed must be unbiased and must not be influenced by officers.
3. If safety is an issue, allow the officer to be in clear view. The healthcare provider should not jeopardize his or her own safety. The shackles and restraints may or may not need to be removed.
4. Listen carefully to the complaints and, if the detainee continues to express complaints, reassess as needed.
5. Provide the detainee with information about required tests, results, discharge instructions, prescriptions, etc. as you would for any other patient, recognizing that follow-up and compliance may be impossible. Consider calling the correctional facility to update the healthcare provider of the detainee's medical management needs and to assure adequate follow-up.
6. Instruct the accompanying officer on any medical or physical limitations that the detainee (i.e., shoulder dislocation) may have that would influence the way the detainee is positioned or shackled.
7. The frequency of the treatments and follow ups if needed should be communicated to accompanying officer.
8. All emergency department staff who services the inmate population should know the communication options with the correctional facility.
9. If opioids are needed for pain, then they should be administered same as you manage any other care. There should be no bias when managing pain in this population.

10. If controlled substance is recommended, this should be done in close communication with the correction facility as there might be limitations/restriction on using those medications after discharge at the correction facility. Good communication is essential to make sure there is a good and continuous care in the hospital and after returning to the correction facility.
11. As with all patients, maximum patient privacy to the extent possible should be maintained.
    (a) Like non-incarcerated adults, patients have the right to choose their own surrogate decision maker or healthcare power of attorney.
    (b) The main difference is that a provider should get permission from the warden to contact the surrogate decision maker.
    (c) A provider should determine medical treatment, discharge dates, level of care without any undue influence from the correctional facility [3].
    (d) Provide multidisciplinary pain management using non-opioid medications, physical therapy, pain psychology, infusion therapy and regional anesthesia.

When a prisoner is admitted to acute care or inpatient settings, it poses impact on the delivery of health care, as security requirements are as important as medical requirements of the prisoners. With the information that the in prisons there is no access to the pharmaceutical benefits scheme the medicines are purchased through contract arrangements. So, when an incarcerated patient is discharged to the prison from inpatient settings, medicines may be changed to alternatives that are available on the approved formulary. Medicines are usually provided to patients daily under supervision and depending on the potential for drug diversion and abuse. Discharge planning is very important for incarcerated patient population and the information provided to the patient and prison staff should be easy to understand, culturally appropriate and may require the use of health workers or an interpreting service. Careful thought of simplifying the medication regimen to meet patients' needs is also a practical consideration when discharging the patient to the prison [4].

36.4 Dealing with Abuse and Addiction

Approximately 75% of people in custody have used illicit substances before incarceration. In correctional facilities there is always a concern regarding the prescription medicines being used as "cash" or barter either voluntarily or under pressure. In the inpatient settings while treating pain in incarcerated patients it is important to keep in mind that the patient will be discharged to jail or prison where medications like opioids, benzodiazepines have high potential for abuse and diversion [5].

As providers it is also important to be aware that patients in correctional supervision or being discharged to correctional facilities from inpatient settings should be encouraged to start and be compliant with potentially lifesaving opioid or opioid agonist treatment. As physicians, we have an important role to play in advocating

for change in both the criminalization of addiction, removing stigma and access to evidence-based, community standards of care for people under correctional supervision [6].

Collaboration with a multidisciplinary team which may include pharmacists, nurses, psychologists, physiotherapists, interpreters, occupational therapists, addiction medicine specialists, psychiatrists, pain management specialists, representatives from the custodial services, physicians and surgeons ensures best care delivery to the patients. This approach is particularly helpful in chronic disease states like chronic pain and palliative care.

In general, a practitioner should approach prescribing a patient to be discharged in custody with the following in mind:

- The basis for a safe and effective treatment is thorough assessment which includes seeking information from GPs, hospitals and other health professionals who have treated the patient.
- The prescription of psychoactive medicines needs to be based on a formal diagnosis.
- It is vital to communicate with others providing care because of the risk of prisoners playing individual clinicians off against one another.
- Always be cognizant of potential drug-seeking behaviors. These include requests for specific drugs, aggressive and unreasonable behaviors, and giving information that is not consistent with objective findings.
- All patients with complex needs should have formal management plans in place [5].

36.5 Summary

- The multidisciplinary, or interdisciplinary, model of pain management as built up on the premise that no single Specialist possesses all of the tools that may be necessary for effective management of difficult cases of chronic pain.
- The consultant and pain medicine providers must necessarily rely upon hospitalists/primary care physicians for referrals and must also have the appropriate resources for invoking treatments that may be outside of his or her own particular discipline {e.g. physiatrist, neurologist, psychologist, psychiatrist, neurosurgeon, anesthesiologist}. This approach is really critical in managing incarcerated patients in a hospital setting.

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Chapter 37
Economic Burden of Pain

Derek Schirmer, Jay Karri, and Alaa Abd-Elsayed

37.1 Introduction

Pain is a pervasive health issue that adversely affects both the patient and society, including loss of productivity, decreased quality of life, and an increased burden on the health care system. Acute pain conditions are often subsequent to traumatic injuries, surgeries, or acute disease states and often resolve with resolution of the inciting physiological disturbances. However, a subset of persons with persons with acute pain conditions often develop chronic pain syndromes, which are defined as persistent or recurrent pain conditions lasting longer than three months [1]. Unfortunately, persons with chronic pain can suffer from varying levels of disability and confer a significant portion of healthcare expenditures [2]. Consequently, early and goal direct management of acute pain conditions is imperative to limit patient suffering, improve functional outcomes, and reduce the prevalence of chronic pain.

Based on the prevalence of chronic pain, a conservative estimate of the annual cost of chronic pain in the United States is approximately $560–635 billion based on direct medical expenses, lost productivity, and disability programs [3]. While precise healthcare costs of acute pain are unclear, the burden of acute pain conditions causing prolonged hospitalization and recurrent emergency room visits is thought to be quite large. Estimate costs of healthcare at the expense of pain condi-

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tions are thought to be roughly $261–300 billion, with the costs of lost productivity being approximately $297–336 billion. These estimates are conservative given that they exclude the cost of pain affecting institutionalized individuals, military personnel, children under age 18, and personal caregivers (such as spouses who miss work while caring for people with pain), as well as the lost productivity of workers younger than 24 and older than 65 [3]. Consequently, a multifaceted approach directed at positively impacting acute pain can in result have significant impacts in ameliorating healthcare burden and improving patient outcomes.

37.2 Stakeholders

The socioeconomic burden of pain is a multifaceted problem with many interrelated stakeholders (Fig. 37.1) who work in concert with one another and are collectively affected by actions of any one party. Changes in this network create broad societal implications. Briefly, the main stakeholders implicated include patient families, the government and society, insurance payors, and healthcare systems and physicians. This network centers around patients suffering from acute pain conditions. Undertreated acute pain can result in prolong hospitalization lengths, recurrent emergency room visits, and even worse patient outcomes [4]. Additionally, persons with chronic pain can often have acute pain exacerbations, which themselves can significantly contribute to disability and employment [5].

In the emergency department, there is pressure on the physicians to maintain patient satisfaction scores as well as appropriately treating the patient. This pressure could lead to increased utilization of hospital resources [5]. Consequently, increased healthcare costs place financial strains on hospitals when patients are unable to pay, and insurance companies do not reimburse expenses. Likewise, insurance companies are also subject to the stress of repeated payments for seemingly avoidable problems. This leads to reactionary actions from insurance companies to deny claims, increase premiums, or adjust care to mitigate costs [6]. These actions cycle back to influence the hospital systems and, ultimately, physician's treatment decisions, potentially resulting in under treatment of patients suffering from chronic pain [5]. With this system in mind, each stakeholder is affected differently. In the next section, the effect on each stakeholder is discussed in more detail.

37.2.1 Families

The social costs of pain affect not only the person in pain but also friends, coworkers, and especially the family. Family members find that their relationship with their loved one changes, and to the extent that they must take on new roles (i.e. caregivers) and greater responsibilities in the family (e.g., grocery shopping, chores, errands),

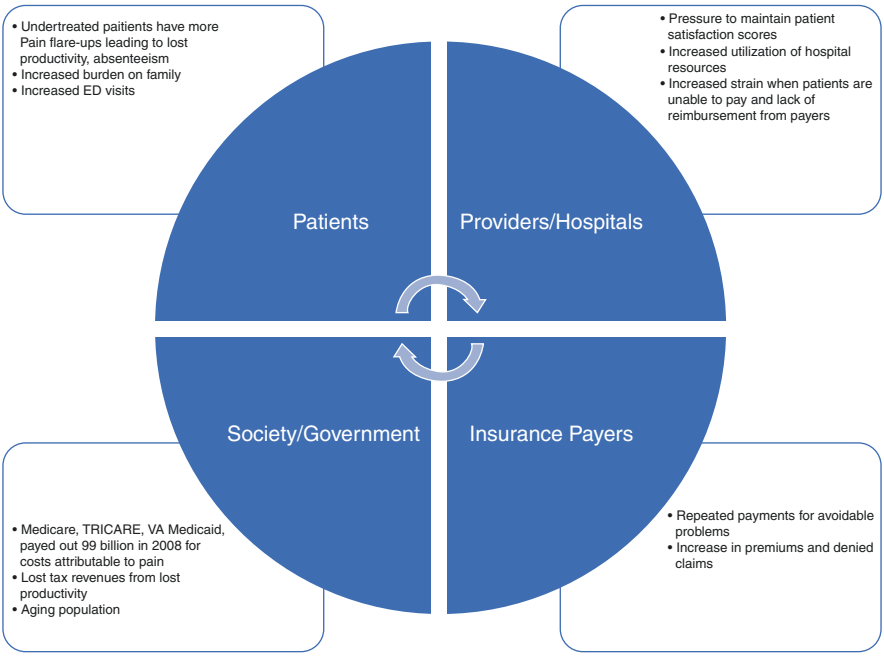

Fig. 37.1 Schematic depicting the interplay amongst the four major stakeholders

the burden on them increases [4]. These familial burdens are expectedly amplified with prolonged hospitalizations and recurrent emergency room visits.

Caregiver burden is an increasingly recognized phenomenon given that it highlights the previously under recognized costs and impacts of caregiving on the providers. Just as acute and chronic pain adversely affects patients, caregivers may be similarly affected by lost wages, increased time off work, and emotional drain as they tend to patients.

37.2.2 Government/Society

The federal Medicare program bears fully one-fourth of U.S. medical expenditures for pain; in 2008, this amounted to at least $65.3 billion, or 14% of all Medicare costs. In total, federal, and state programs—including Medicare, Medicaid, the Department of Veterans Affairs, TRICARE, workers' compensation, and others—paid out $99 billion in 2008 in medical expenditures attributable to pain. Lost tax revenues due to productivity losses compound that expense [7]. Disability from all causes has been estimated to cost $300 billion annually, with the pain-related conditions of arthritis and back/spine problems being the top two causes of disability [8].

37.2.3 Insurance Companies

With an aging population and growing utilization of health insurance plans, insurance companies have had to adapt to mitigate the increased costs. According to Lagoe and colleagues, "Traditional insurance plans have moved toward managed care by adopting features of health maintenance organizations such as utilization controls. As a result, the border between for-profit and not-for-profit insurance is now almost nonexistent" [9]. As a result, all health insurance now constitutes "managed care," as it is the insurer rather than the patient and physician that decides which treatments can be provided [9]. A salient example of how this can lead to disparities between recommended treatments and insurance reimbursement is in insurers' refusal to cover interdisciplinary pain management programs [10]. Numerous studies, meta-analyses, and systematic reviews have indicated that interdisciplinary pain management constitutes the most clinically effective and cost-efficient means of treating most pain conditions [11–15]. The paradox of insurers' refusal to cover interdisciplinary pain management programs is that this practice steers patients toward more expensive and less effective unimodal treatments, ultimately helping neither the patient nor the insurer [10]. A clear example of this phenomenon can be seen in insurance carriers' implied support for chronic opioid therapy for chronic nonmalignant pain. Chronic opioid users represent only 0.65% of the population, yet file 4.56% of all health insurance claims [16]. A significant portion of these healthcare costs are resultant of recurrent provider and emergency room visits. The dramatic increase in prescription opioid abuse has resulted in substantially higher costs among those covered by private insurance as well as by Medicaid [17]. Despite these recently published data, third-party payers generally remain willing to cover prescription opioid analgesics, with coverage for and availability of interdisciplinary chronic pain management in the United States rapidly declining [6].

37.2.4 Hospitals/Physicians

Pain is the most common reason patients visit the emergency department for care [18]. A study by Downey et al. found that a reduction in perceived pain levels directly corresponds to several indicators of customer service [5]. Patients who experienced pain relief during their stay in the Emergency Department had significant increases in distress relief, rapport with their doctor, and intent to comply with given instructions [5]. Based on these studies, it would seem reasonable that Emergency Department physicians would be influenced to adequately treat pain in the setting of the Emergency Department visit. However, there is confusion among providers regarding the proper clinical use of opioid medications and their potential for misuse, abuse, and diversion [19]. Also, many clinicians do not recommend interdisciplinary pain management services to their patients [19]. There is rarely a uniform response to pain among practitioners as acute pain, though severe, is not

necessarily an emergency. Furthermore, current evidence indicates that there is a lack of implementation of, and nonadherence to, evidence-based guidelines among practitioners [20].

37.3 Determinants of the Economic Burden of Care

The annual economic costs of pain can be divided into two main categories: (1) the direct costs of medical care due to pain and (2) the indirect costs of pain due to lower productivity associated with lost days and hours of work. These categories accommodate the various factors that add to the growing economic burden of pain management.

Direct cost factors include recurrent emergency department visits for opioid overdose as well as acute pain syndromes, which can vary in etiology from acutely worsened chronic pain conditions to traumatic injuries to other acute pain states. Additional direct care costs attributable to acute pain includes extended hospitalizations and increased medical costs for co-morbid conditions in persistent pain patients [7]. While there are high utilization costs associated with acute pain, more critically: pain is being treated inadequately. This phenomenon feeds back into other direct health care costs, such as overutilization of the Emergency Department.

Indirect cost factors include absenteeism from acute pain conditions. Absenteeism accounts for the highest lost revenue in the form of lost productivity. A study performed in 2003/04 estimated that the impact of arthritis on lost productive work time amounted to $7.11 billion, but with 66% of this attributed to the 38% of workers with pain exacerbations [21]. In addition to the impact of absenteeism, pain also has a significant effect on worker productivity [22]. A study found that common pain conditions resulted in lost productivity despite being present at work (also referred to as presenteeism) amounting to $61 billion per year, of which 77% was attributed to reduced performance and not work absence [23].

In persons with chronic pain and acute pain exacerbations, quality of life is often compromised. A diminished quality of life can impair the ability to perform daily activities, work, and maintain friendships and family relationships [19, 24]. This strain on everyday life results in emotional distress and is consistently linked to an increased risk for depression with or without concurrent anxiety disorders [25]. As discussed earlier, these direct and indirect costs are shared by all the stakeholders in some capacity.

37.4 Proposed Strategies to Mitigate the Healthcare Burden

As discussed earlier, the actual economic burden attributable to pain is likely underestimated, stressing the need for more accurate data. As proposed by Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and

Research, there is a need for more consistent data on chronic pain [19]. Specifically, the future data should be focused on monitoring changes in prevalence and incidence of chronic and acute pain, the magnitude of interference with activities of daily living and work, utilization of clinical and social services, costs of pain and pain care including indirect costs, the effectiveness of treatment and comparative effectiveness of alternative therapies. Based on appropriate data, the next recommendation is to create a comprehensive population health level strategy for pain prevention, treatment, management, time frames, and resources. This strategy should: Describe how to establish inter-governmental relations to promote community-wide approaches to pain in subgroups of America, improve pain assessment and management programs within the federal government, proceed in cooperation with the Interagency Pain Research Coordinating Committee and National Institutes of Health's Pain Consortium and reach out to private-sector participants, and promote public awareness about chronic pain and the role of self-care in its management.

There are several notable barriers to address when considering a comprehensive strategy. Foremost is the considerable lack of awareness of the socioeconomic burden associated with pain among all stakeholders. At the healthcare provider level, there is an urgent need for education and training of healthcare providers to address the gaps in knowledge and competencies in the care of individuals with pain [20].

Responsibly managing a patient's pain requires a degree of self-management to prevent pain flares and minimize functional impairment. It is often not utilized by patients because of the lack of patient education [19]. Even when providers are knowledgeable of alternatives to opioids in pain management, they rarely have time to explain chronic management in an emergent setting. Patient education is, therefore, a critical component of decreasing inappropriate healthcare utilization. It should focus on the prevention of common types of pain, timing, and methods of self-treatment, knowing the appropriate time to consult a physician, treatment goals, and access to other resources and support [24].

An exciting development in providing easy and cost-effective access to consultant pain medicine expertise is telemedicine [26]. Telemedicine can decrease the number of "no shows to appointments," hospitalizations and emergency department visits for patients who previously had no access to care [26]. While the efficacy of these telemedicine programs still needs to be determined, it provides an innovative avenue in bridging disparities in the healthcare of these patients.

As discussed earlier, health care organizations and payers have reimbursement policies that may limit frequent physician visits and restrict comprehensive assessments [10]. The underuse of interdisciplinary management may also hinder patient-centered care [10]. Recent data has indicated that while interdisciplinary management is not only the preferred treatment method of choice but it also significantly reduces cost. Additionally, clinician's treatment plans are increasingly influenced by drug insurance plan formularies [27]. These reimbursement policies require robust revision to provide optimal, evidence-based pain care [28].

37.5 Summary

- The annual cost of pain is estimated to be $560–635 billion based on direct medical costs, lost productivity, and disability programs.
- Pain conditions overall are detrimental to several key stakeholders including patients, families, physicians, healthcare systems, insurance companies, and society as a whole.
- Acute pain management often warrants a multifaceted strategy in order to effectively treat and thereby, prevent prolonged hospitalizations and recurrent provider and emergency room visits.

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Chapter 38
Patient with Multiple Allergies/ Intolerances

Lee Kral, Justin Wikle, and Rahul Rastogi

38.1 Introduction

It is not uncommon for patients in the hospital to report long lists of drug allergies and intolerances, especially if they have been exposed to a large number of medications to treat complex disease states or had multiple hospitalizations. An estimated 15.1% of hospitalized patients experience adverse drug reactions (ADR's) [1]. Unaddressed ADR's can lead to reduced quality of life, delayed or suboptimal treatment, unnecessary investigations, increased morbidity, and possibly mortality [2]. It is up to the clinician to sort through these to determine if they are true allergies or if individual agents should simply be avoided to prevent adverse effects.

The spectrum of medication-related adverse reactions ranges from intolerance to simple histamine-related immune reactions to anaphylaxis. This spectrum also reflects the severity of consequences that a patient will face if the reaction occurs. Adverse drug reactions are classified by the World Health Organization as predictable (Type A) or unpredictable (Type B) [3].

Multiple adverse medication reactions are classified as either Multidrug Intolerance Syndrome (non-immunogenic) or Multiple Drug Allergy Syndrome (immunogenic).

Antibiotics, NSAIDs and anesthetics are the most frequently reported drug allergies. Self-reported drug allergies are reported 8.3% of the time, mostly cutaneous (68.2%) and anaphylactic 10.8%. They are more commonly reported in females, adults and inpatients [4]. The Gell and Coombs classification is used to designate the type of immunologic reaction including IgE mediated (Type I), cytotoxic (Type II), immunocomplex (Type III) and delayed cell mediated (Type IV). This is used in

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the evaluation of adverse effects and leads to either further testing and/or modification in the analgesic plan.

This chapter will focus on evaluating analgesic intolerances and hypersensitivities, identifying which patients may need a consultation with an allergy/immunology specialist for further testing, and how to move forward in a given scenario.

Patient scenario: You are asked to see a 63-year-old female (BMI 31) who presented for elective right shoulder arthroscopy with rotator cuff repair and biceps tenotomy. She reports that she has allergies to multiple opioid medications. At home she has been taking gabapentin, naproxen and tramadol. She notes that for a previous surgery that she received peri-operative methadone (unknown dose and regimen) and fentanyl without any problems.

38.2 Pathophysiology

Adverse drug reactions (ADR's) are generally classified as predictable (Type A) or unpredictable (Type B). Multiple adverse medication reactions are classified as either Multidrug Intolerance Syndrome (non-immunogenic) or Multiple Drug Allergy Syndrome (immunogenic).

Predictable reactions are seen in about 80% of all ADR's [3]. These reactions are commonly dose-dependent and occur as the result of overdose, known side effects, secondary effects or drug interactions. They may arise from disturbance of a body system that affects the drug such as the effects of liver disease on metabolism of hydrocodone (pharmacokinetic), or the effects of the drug on a body system such as GI upset with NSAIDs or sedation with a gabapentinoid (pharmacodynamic). They also may be caused by a drug-drug or drug-disease interaction such as reduced clearance of morphine metabolites in the setting of renal compromise. Predictable changes in physiologic status in the acute care setting (e.g. blood loss and dehydration with surgery) can be anticipated and planned for.

Unpredictable or idiosyncratic reactions are associated with an estimated 20% of ADR's [3]. True IgE hypersensitivity reactions comprise about 6–10% of ADR's [5]. They generally are not related to dose and may occur at a very low dose without any obvious shift in pharmacokinetics or pharmacodynamics. Anaphylactoid reactions are caused by release of inflammatory mediators from mast cells or basophils without causing an IgE-mediated reaction (e.g. radiocontrast media). If a patient experiences a possible anaphylactoid reaction it should be evaluated, and a plan should be developed if the agent(s) may be used again in the future. The reactions may also be idiosyncratic reactions caused by underlying abnormalities of metabolism, excretion or bioavailability.

Allergic reactions are classified with the Gell and Coombs system of hypersensitivity [2]. Type I reactions are IgE-mediated reactions that cause release of histamine and other mediators from mast cells and basophils (like anaphylaxis to penicillin). Type II reactions are cytotoxic and related to IgG or IgM antibody binding to cell surface antigens, causing complement fixation (like NSAID-induced

Table 38.1 Hypersensitivity reactions with analgesics

Type of reaction	Cause	Clinical signs/ symptoms	Timing of reaction	Examples of analgesics	Management
Type I	Drug-IgE complex binds to mast cells, releasing histamine and inflammatory mediators	Urticaria, pruritis, angioedema, bronchospasm, anaphylaxis	Minutes to hours post-exposure	NSAIDs (ASA, diclofenac, ibuprofen, naproxen)	– Stop drug – Steroids, epinephrine, antihistamines
Type II	IgG or IgM antibodies bind to drug-hapten coated cells	Neutropenia, hemolytic anemia, thrombocytopenia	Varies	NSAIDs	– Stop drug – Steroid – Transfusion
Type III	Immune-complex with drug causing complement release and inflammation	Rashes, arthralgias, lymphadenopathy, fever, malaise, hypotension, glomerulonephritis,	1–3 weeks post-exposure	Ibuprofen Oxycodone Bupropion	– Stop drug – Symptoms resolve in 4–5 days – Steroids, antihistamine
Type IV	Delayed MHC presentation of drug to T-cells with release of cytokines and inflammatory mediators	Contact dermatitis, rash, Stevens-Johnson Syndrome, toxic epidermal necrolysis, DRESS	2–7 days post-exposure	Lamotrigine Carbamazepine NSAIDs Lidocaine Levetiracetam Zonisamide	– Stop drug – Steroids – Supportive care

hemolytic anemia). Type III reactions are immune complexes that deposit in tissues with complement activation and inflammation (like ibuprofen or oxycodone). Type IV is a delayed type hypersensitivity reaction mediated by cellular immune mechanisms (like carbamazepine or lamotrigine). See Table 38.1 for examples of these reactions.

Multiple drug intolerance syndrome (MDIS) is defined by multiple nonimmune-mediated adverse reactions to structurally unrelated drugs. Common reactions include rashes, GI problems, headaches, cough, myalgia and fever. These intolerances are usually self-limiting and resolve upon dose reduction or discontinuing the medication. While not usually dangerous, they may certainly be uncomfortable for the patient [6].

Multiple drug allergy syndrome (MDAS) is defined as a patient with adverse reactions to two or more structurally unrelated drugs caused by an immune-based mechanism [7]. Histamine-related reactions are mostly cutaneous, but also may involve the blood components, kidneys, liver, cardiopulmonary, or musculoskeletal systems. These are more uncomfortable than dangerous and are not anaphylactic (such as flushing and itching with morphine use). These are typically relieved by stopping the medication in question and administering an antihistamine, steroid and/or epinephrine. Anaphylaxis is the most immediately dangerous reaction but also relatively rare, particularly with analgesics.

38.3 NSAIDs

NSAID-induced reactions are estimated to cause about 25% of drug reactions. These may be immune-mediated or nonimmune-mediated. Generally, there are two different types of reactions: the cross-reactive type and the single drug-induced type [8]. The cross-reactive type of reaction is a nonimmunological reaction where two NSAIDs with different chemical structures cause the same reaction. This is typically caused by inhibition of the cyclo-oxygenase 1 (COX1) enzyme in the inflammatory pathway, leading to overproduction of leukotrienes in the respiratory and inflammatory pathways. More than 50% of NSAID-induced reactions are caused by aspirin and other potent COX-1 inhibiting NSAIDs. Weak COX-1 or selective COX-2 inhibitors are usually well tolerated in patients with cross-reactive types [9].

The single drug-induced type of hypersensitivity is attributed to a single NSAID or chemically-related NSAIDs and may cause Type I or Type IV reactions. The propionic acids like ibuprofen, and naproxen are most commonly associated with this. These patients tend to do fine with NSAIDs in different structural families [9]. See Table 38.2 for details on these types of reactions [8].

38.4 Opioids

ADR's with opioids are commonly reported but true hypersensitivity is thought to be rare. Most reactions are considered to be due to mast cell degranulation. In a study of hospitalized patients reporting an opioid allergy, it was determined that 50% of the reactions were actually intolerances. Patient historical reports of allergy to opioids were not significantly associated with IgE-mediated reactions to the same

Table 38.2 NSAID-induced adverse drug reactions [8]

Type of reaction	Clinical presentation	Timing	Cross-reactivity	Mechanism
NSAIDs-exacerbated respiratory disease (NERD)	Bronchial obstruction, dyspnea, nasal congestion	Immediate or within several hours	Cross-reactive	Non-allergic COX-1 inhibition
NSAIDs-exacerbated cutaneous disease (NECD)	Wheals, angioedema	Immediate or within several hours	Cross-reactive	COX-1 inhibition
NSAID-induced urticarial/angioedema (NIUA)	Wheals, angioedema	Immediate or within several hours	Cross-reactive	Unknown, possibly COX-1 inhibition
Single-NSAID induced urticaria/angioedema or anaphylaxis (SNIUAA)	Wheals, angioedema anaphylaxis	Immediate or within several hours	Allergic Non-cross reactive	IgE-mediated (type I reaction)
Single-NSAID-induced delayed reactions (SNIDR)	Various symptoms, SJS/TEN, fixed drug eruption, nephritis	Delayed onset (>24 h post-exposure)	Allergic Non-cross reactive	T-cell mediated (type IV reaction)

or any other class. Cross-reactivity ranged from 0 to 6.7%. A total of 92.5% of patients tolerated re-administration of opioids with 1.6% developing a possible allergic reaction [10].

Reactions to opioids fall into three classifications—(1) those that have no immunologic component, (2) anaphylactoid reactions and (3) immune-mediated reactions. Those that are not immune reactions include sedation, constipation, nausea, vomiting, urinary retention, respiratory depression, delirium, etc. Anaphylactoid reactions include itching, urticaria, hypotension and bronchospasm. These usually occur soon after an opioid dose. The reaction is usually caused by mast cell degranulation and histamine release. These symptoms are usually mild and self-limited and may or may not recur upon re-challenge with the same medication and does not preclude use of alternative opioid agents. Immune-mediated reactions may be localized to the skin (vesicular eruptions, eczema or erythroderma) or anaphylactic reactions, causing the immediate release of immune mediators driven by IgE. This systemic reaction may lead to bronchospasm, hypotension and death [11]. It is thought that synthetic opioids are less likely to cause a hypersensitivity reaction than natural opioids.

38.5 Anticonvulsants

Anticonvulsant hypersensitivity syndrome (AHS) or drug reaction with eosinophilia and systemic symptoms (DRESS) is a reaction that is reported at a frequency of 1:10,000–1:1000. This reaction is most commonly associated with the aromatic drugs like carbamazepine and oxcarbazepine, phenytoin and barbiturates (phenobarbital and primidone). In addition to the cutaneous reactions, patients may have fever, eosinophilia, liver enzyme elevation, and lymphadenopathy but may be life-threatening and involve multiple organ systems. The immune mechanism is currently unknown but may be T-cell mediated or a toxic reaction to metabolites. Cross reactivity rates among aromatic anticonvulsants may be as high as 80% so these should be avoided. Other drugs that have been associated with this reaction are tricyclic antidepressants, dapsone, allopurinol and sulfonamides, and cross-reactivity has been seen with the aromatic anticonvulsants and amitriptyline and doxepin. Non-aromatic agents such as lamotrigine or gabapentinoids have been recommended [12].

Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are part of a spectrum of immune-mediated reactions to medications. Historically the anticonvulsants have been one of the most frequent classes of medications associated with these reactions. Analysis of the US FDA Adverse Effect Reporting System from 2014 to 2017 evaluated all anticonvulsants and noted that these agents were implicated in 19.1% of the SJS/TEN reactions, more than two times greater than with NSAIDs. The specific agents with the highest incidence included lamotrigine (53.5%), carbamazepine (11.1%) levetiracetam (7.1%) and phenytoin (7.1%), valproic acid (3.5%), clonazepam (4.0%), and zonisamide (3.5%) [13].

38.6 Antidepressants

Cutaneous reactions are the most common allergic reactions seen with antidepressants. These can range from erythema multiforme (EM), SJS, TEN, acute generalized exanthematous pustulosis (AGEP) and drug-induced hypersensitivity syndrome (DIHS) or DRESS, as mentioned above. They do not seem to be related to receptor activity. Risk factors for these reactions include young children and the elderly. Cross-reactivity within a class (e.g. SSRI's) has been suggested. An EM reaction will usually resolve when the offending medication is stopped. EM has been reported with trazodone and bupropion as well as sertraline. SJS and TEN have been reported with the SSRI family of agents including fluoxetine, paroxetine, sertraline, as well as bupropion and mirtazapine. AGEP is rare and has been reported after taking amoxapine and SSRI's. DRESS has been reported for both tricyclics and SSRI's [14].

38.7 Local Anesthetics

Patient report of allergy with local anesthetics is typically adverse effects such as syncope. True hypersensitivity is rare and has not been associated with any type of immunologic reaction.

The issue of allergy in local anesthetics is complicated by the presence of preservatives (e.g. methylparabens) and antioxidant stabilizers (e.g. bisulfites) in vials of injectable solutions. Local anesthetics that have an ester linkage (e.g. procaine, benzocaine, cocaine) are derived from para amino benzoic acid (PABA) and hydrolysis liberates a component that is immunogenic. Local anesthetics with an amide linkage are not associated with these reactions related to PABA. The bisulfites that are added to solutions containing vasopressors (like epinephrine) for stabilization have also been implicated in allergic reactions. Since they are also used to keep brightly colored produce looking fresh, patients may report similar sensitivities to these. There is no cross-sensitization between amide and ester local anesthetics.

38.8 Antibiotics

Antibiotics are commonly used in the surgical and procedural pain management setting. Allergic reactions to penicillin is estimated to be about 10% in those who report sensitivity. Clinicians should avoid penicillin if possible. Carbapenems, monobactams and second or fourth generation cephalosporins may be considered. However, it is best to have an allergist evaluate these classes of anti-infectives with skin testing. If a penicillin is absolutely necessary, desensitization should be

considered. Allergic reactions with cephalosporins are usually limited to cutaneous rashes, though there is a small percentage of cross-reactivity between first generation cephalosporins in patients who have a penicillin allergy. Sulfonamides are also commonly associated with allergic reactions, including cutaneous reactions, SJS, and TEN. This is especially important in the immunocompromised patient as trimethoprim/sulfamethoxazole is necessary for prophylaxis of opportunistic infections.

38.9 Risk Factors

One of the risk factors for an immune-mediated reaction is previous immune reactions to structurally similar medications. This is notable for antibiotics, but less so for analgesics [15, 16]. See Table 38.3 for information about patient and drug-related risk factors.

Patients with MDIS had a higher rate of health care utilization, higher medication use and a higher incidence of new drug "allergies". Patients with more than one drug allergy, older age (e.g. 60 years of age), females, and those with higher BMI were more likely to report ADR's [6].

Patient scenario: EI has several risk factors including female gender, older age and higher BMI. She denies any family history of drug allergies, but she does not have any siblings or children. She can't recall her parents ever mentioning drug allergies.

38.10 Evaluation [17]

- Evaluating the patient with multiple reported ADR's, including possible drug allergies, includes an extensive health and family history, with special attention paid to any possible allergic reactions. The history will help confirm whether the

Table 38.3 Risk factors for allergic reactions[15, 16]

Patient-related	Drug-related
Women > men	High molecular weight and hapten-forming drugs
Age: young/middle age adults > infants/elderly	Route of administration: topical > IV/IM/oral
Genetic polymorphisms and predisposition (e.g. atopy)	Dose: frequent/prolonged use > single dose
Viral infections (HIV, herpes virus)	
Previous reaction to drug or structurally similar medications	
Food allergies	
Other co-morbidities (e.g. asthma)	

Table 38.4 Evaluation of a medication/reaction history

Route of administration	Parenteral administration more likely to cause reaction compared to oral
Number of doses taken before reaction	A reaction within the first 1–2 doses is more indicative of an immune-mediated reaction compared to having taken multiple doses
Prior exposure to drug or similar drugs	Immune-mediated reactions are more likely to occur with a previous exposure. If the patient has tolerated a similar medication (e.g. NSAID, opioid) the patient may not have a true allergy or has lost sensitivity
Time between last dose and onset of symptoms	IgE-mediated reactions usually occur within 2–4 h
Symptoms resolved after stopping drug	If symptoms persist, they may not be related to the drug
Length of time since reaction	Reactions in the remote past (childhood) may not be remembered well, not thoroughly evaluated at the time, or the patient may have lost sensitivity
Other concurrent drugs	Concurrent drugs may alter the presentation or severity of a reaction (e.g. prednisone)
Systems involved in the reaction	Cutaneous reactions, systemic symptoms (e.g. fever, bronchospasm)
Management required to treat the reaction	Self-managed or required hospitalization

patient is at risk for possible allergic reaction. For example, a patient with atopy is predisposed to having allergic reactions. Presence of risk factors should heighten the clinician's awareness.

- Obtain a detailed drug and drug allergy history. See Table 38.4 for a list of factors to consider when interviewing patients. Identify any medications that may require skin testing or require a drug challenge.
- It is also important to determine how necessary each of the medications are in the treatment of the patient's pain, if there are reasonable alternatives, or if an allergist needs to be involved.
- Investigations—There are several approaches to identifying drug allergies, however skin testing is the only validated method to detect true antigenic markers. It has only been validated for penicillin but may be considered for other medications using a very low concentration of drug in question. If the skin test is positive, it is sensitive enough to suggest that providers should avoid structurally similar agents. However, the specificity is not high, so a negative skin test does not rule out a possible IgE-related allergy. Another method is to give a test dose under close observation, or a drug provocation test (DPT). Of 98 patients referred for DPT, only 15% were diagnosed with opioid allergy. Angioedema and hypotension were more frequent in those with a positive DPT than those with negative DPT, Table 38.5 [18].

Table 38.5 Evaluation of a patient with possible drug allergies

Conduct a physical exam and history, identify type of pain that the patient has (neuropathic, musculoskeletal, etc.)
Conduct a thorough review of other chronic disease states
Conduct, with the patient, a thorough medication and allergy history (see Table 38.4)
Identify medications that may require skin testing or require a drug challenge
Review the evidence available regarding the treatment of the type of pain the patient has (non-pharmacologic, interventional, pharmacologic, etc.)
Determine how necessary the medication is, if there are reasonable alternatives, or if an allergist needs to be involved
Consult with allergist to determine what testing needs to be done
Develop a list of medications that are safe to use, a list of meds to avoid and a list of meds that can be considered for future testing or induction of drug tolerance
Review these with the patient, to determine if there are any concerns. Educate the patient on testing and desensitization processes that may need to be done for a given treatment
Efficacy and adverse effects should be reviewed on a daily basis while in the hospital, adjusting dose and regimen as needed
Discharge planning should include communications with the patient's local team (provider, pharmacy, etc.). Medical record list of allergies and intolerances should be updated with current information

- Develop a list of medications that are safe to use, a list of meds to avoid and a list of meds that can be considered for future testing or induction of drug tolerance.

Table 5 Patient scenario: EI reports the following as part of her history

Medication	Reaction noted in medical record	Clarification of reaction
Codeine	*Pruritis, anaphylaxis*	*Denies pruritis, but had throat tightness with cough medicine*
Hydrocodone	*Pruritis*	*"Doesn't tolerate" but cannot recall any throat tightness*
Hydromorphone	*Anaphylactic shock*	*Didn't recall having any problems*
Morphine	*Upper airway edema, anaphylactic shock*	*Received several times in the past with itching and a little throat tightness*
Oxycodone	*Anaphylactic shock*	*"Doesn't tolerate" but cannot recall any throat tightness*
Oxymorphone	*Not noted*	*Had a "terrible" reaction but cannot recall any throat tightness*
Cortisone	*Injectable—hives* *Topical—no reaction*	*Confirmed*
NSAIDs		*No reactions*
Local anesthetics		*No reactions*
Anticonvulsants		*No reactions*
Antidepressants		*No reactions*
Fish-containing foods	*Hives, controlled with antihistamines*	*Confirmed*

38.11 Treatment

Pain management in the setting of multiple allergies or intolerances necessitates a prioritization scheme.

- First—is the medication necessary or can an alternative be used? In the case of a major surgery the patient will need for an opioid for adequate analgesia. In a patient with multiple reported opioid allergies this will need to be addressed prior to the case. If there is a true analgesic allergy or even an anaphylactoid reaction, clinicians should avoid possible offending agents. It is unusual in the analgesic field that there would not be a reasonable alternative. If an alternative is not possible, and the allergy appears to be real, an allergist should be consulted before proceeding with management.
- Non-pharmacological management is always first-line therapy for both acute and chronic pain and avoids analgesics altogether. In patients with multiple drug sensitivities, these will need to be optimized. Options include everything from heat and ice to aromatherapy, music therapy or relaxation/meditation techniques.
- Interventions that avoid any sensitivities would be ideal if the situation is amenable. Regional or neuraxial techniques for surgical patients are an excellent choice if possible.

Patient scenario: EI reports that she tolerates fentanyl and methadone and is currently taking tramadol. She is having an arthroscopic procedure in the ambulatory surgery center (with 23-h observation) that will not require large doses of opioid afterward. The team utilized a multimodal regimen including an interscalene block with ropivacaine for the case and overnight, scheduled acetaminophen, continued her home gabapentin dose, restarted her naproxen and doubled her tramadol dose to 100 mg every 6 h. Fentanyl was used as part of her anesthesia regimen and was available IV as needed on the floor, which she did not use. If she had undergone a larger surgery (e.g. total arthroplasty) the tramadol may not have been adequate for analgesia. The team could have utilized either oral hydromorphone (since she did use it in the past) or tapentadol, which she had not used, but is also synthetic.

38.12 Pain Assessment Tools

The usual pain assessment tools may be used in these patients, but clinicians also need to educate patients, families and bedside caregivers of the signs and symptoms of a reaction—allergic or otherwise.

38.13 Challenges in Management of Pain While in the Hospital

Challenges in the hospital include patient factors, provider factors and system factors. The patient may be reluctant to try anything similar to what they had a reaction to. In this case, it is important to educate the patient about drug allergy and/or

intolerance, why they likely occur (or if idiosyncratic) and possible cross-reactivity (or lack of cross-reactivity). Providers may be reluctant to prescribe any drug in a class that the patient has reported a drug intolerance to, for fear of an allergic reaction or causing the patient to be upset. Clinicians may also undertreat pain by using second-line therapies. If the patient appears to have a true allergy or even an anaphylactoid reaction, consulting an allergist for skin testing or desensitization would be time consuming but quite possibly necessary for safety. Again, the patient needs to be educated about the importance of this process. If a non-formulary medication is deemed necessary, there may be paperwork and requests to be processed, and the medication may need to be special ordered, which could take several days.

38.14 Discharge Plan for Pain Management

Discharge planning should include updating the allergy/intolerance list in the electronic medical record with supporting documentation about any reactions and any evaluations undertaken to clarify this. The patient may need to be referred to an allergist for further evaluation to plan for the future. A copy of this information should be given to the patient and communicated effectively to the patient's primary outpatient team. It has been shown that this process can reduce ADE-related visits to the ED and readmissions [19].

The discharge process should include a discussion with the patient and caregivers about management of pain after discharge and what information needs to be kept on the patient in case of an emergency. The patient may need a medical alert bracelet or necklace to notify providers of any drug allergies that might be encountered in the urgent care setting. It is ideal to have the patient involved in the decision-making process, called shared decision making. This can be especially helpful when updating allergy/intolerance lists so that the patient knows which medication reactions are drug intolerances and which may be true allergies.

Patient scenario: EI was discharged with naproxen, gabapentin and tramadol. Her allergy list in the medical record was updated to reflect her clarified information.

38.15 Summary

- Identify allergies and their extent in all patients you are treating. Make sure you are using treatment modalities that will not cause allergy or has cross allergy with patient documented allergies. It is helpful to have a plan in place for managing those patients so it can be quickly implemented when patient is admitted to the hospital for pain managagement at any setting.

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Chapter 39
Patient with Pancreatitis and Organ Related Pain

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39.1 Introduction

The patient with organ related pain can present a diagnostic and treatment dilemma for even the most astute clinician. In the workup and management of such patients, it is important to understand the underlying pathophysiology and etiology of the disease. In addition, a solid foundation of knowledge concerning the underlying mechanisms of its management is important to keep in mind. This chapter will present the current medical understanding of the diagnosis and workup as well as a summary of some current evidence-based management options for the patient with organ related pain.

The global burden and incidence for something as broad as "pain" are surely difficult to elucidate. Research on the global burden of pain has largely been limited to musculoskeletal pain up until the last decade or so [1]. Since that time, more work has been done to demonstrate just how prevalent and burdensome organ related pain can be. In a 2003 WHO study, 22% of primary care patients reported having chronic pain; defined as persistent pain for a period greater than 6 months [2]. In another study conducted in the United Kingdom concerning the epidemiology of chronic pain, it was found that up to half of experimental subjects will have experienced an episode of pain lasting at least 1 day over the course of a month [3]. It is clear that chronic pain presents a substantial disease burden to the average patient population.

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The incidence of chronic pain amongst patients presenting to inpatient and outpatient services makes proper workup of these patients an important priority. An important issue many epidemiologists have found when studying chronic pain is being able to predict which patients' pain will evolve into chronic cases [3]. This issue points to the necessity of developing guidelines for early management that would not only optimize patient care but cost effectiveness as well [3]. This is further highlighted by the fact that in the United States, pain-related care expenses far exceed those for other diseases such as cancer, heart disease, and diabetes [4].

39.2 Pathophysiology

Before we can understand the workup and management of organ related pain, it is important to understand the underlying pathophysiology of the disease process we are treating. Much of our present understanding of mechanisms of pain centers upon somatic pain whereas the study of visceral pain has been somewhat neglected [5]. This is most likely due to the complications associated with the study of visceral structures as compared to the relative ease of studying somatic structures [5]. Organ related pain or "true visceral pain" is commonly described as diffuse and poorly defined, owing to the low density of visceral innervation and diverging of visceral afferents within the central nervous system [5].

The basics of pain transmission can be boiled down to a sequence of events involving four processes: *transduction*, *transmission*, *modulation*, and *perception* [6]. *Transduction* occurs in peripheral terminals of afferent neurons generating an action potential which, if sufficient, will *transmit* more action potentials via spinal neurons through the nervous system including projections to brain structures such as the thalamus and brainstem [6]. *Modulation* describes the process by which these signals may be altered as they progress along the pain pathway and *perception* is the final stage by which a somatosensory signal results in the sensation we describe as "pain."

Peripheral visceral neurotransmission is an important topic to highlight in the pathophysiology of visceral pain. Visceral innervation has what is known as a dual sensory innervation, that is, visceral afferents travel through both sympathetic and parasympathetic nerves [5]. This becomes important when studying the physical manifestations in the symptomatic patient with visceral pain. For example, the activation of chemoreceptors or stretch receptors in various organs is not consciously felt, however, sensory afferents innervating the gastrointestinal tract may cause a conscious sensation of pain or fullness when activated [5].

Another important aspect of the pathophysiology of visceral pain is viscerosomatic convergence. This refers to the convergence of visceral and somatic components of the afferent inputs to the central nervous system [5]. This is believed to account for the referred pain felt during many organ-related pathologies where the stimulation of visceral neurons may converge with somatic pathways and cause somatic pain [5]. The "Brain-gut axis" is another proposed model linking portions

of the brain with neuroendocrine centers, the enteric nervous system, and parts of the immune system [5]. This may represent a mechanism for the autonomic dysregulation of the digestive system seen with visceral disorders such as irritable bowel syndrome.

Each of these neural pathways may explain some of the manifestations of visceral pain we see in the patient we care for. Visceral pain is known to have a "temporal" clinical evolution manifesting as different stages as the disease progresses [5]. Pain from different organs can present differently; for example, bladder lesions can refer to the perineal area and heart lesions to the left arm [5]. Pain can therefore be referred to somatic pathways as a disease progresses. As previously mentioned, visceral pain is also associated with autonomic phenomena, so a patient may presents with pallor, diaphoresis, nausea, and changes in vital signs such as temperature, heart rate and blood pressure [5].

Another phenomenon to be aware of is visceral hyperalgesia, or an enhanced pain response. This is usually due to persistent stimulation of visceral nociceptors, sensitizing them and reducing thresholds for activation, compounded by storms of inflammatory mediators [5]. This phenomenon has been shown with various human trials demonstrating somatic pain of the chest wall through electrical stimulation of the esophagus as well as introducing acid and capsaicin to the distal esophagus in order to stimulate rectal somatic hyperalgesia [5]. "Interoception" describes the unique sensation of awareness of the physiologic status of the body. It is believed that this awareness stems from an evolutionary adaptation allowing us to maintain homeostasis and avoid injury [5]. Therefore, a patient with visceral pathology may not only present with visceral pain but feelings of physical and emotional distress [5]. The complex neural pathways that drive this awareness are subjects of continuing research.

39.3 Diagnosis

The diagnosis of visceral organ related pain can be approached a number of ways. In this chapter, we will utilize an anatomical approach as we consider various disease processes of the chest, abdomen, and pelvis as well as their generalized management. This, of course, is not a complete list of diagnoses but rather a guideline and patients' workups should be individualized based on the most current guidelines at presentation. This analysis will also focus on the adult patient as many clinical manifestations in the pediatric population may differ. Visceral pain is commonly described as "poorly localized" [7]. It is believed to be a result of nociceptor stimulation as a result of organ distention, stretching, or ischemia [7]. Some other general characteristics of visceral pathology include a "nonspecific or whole-body motor response", a strong autonomic response, sensitization of somatic tissues, and strong affective responses [5].

Visceral chest pain can represent a wide array of pathology. Visceral pain from the heart, or angina pectoris is the classic case of visceral chest pain [8]. It is described as a dull, poorly localized, retrosternal pain that can classically radiate to

the neck or left arm and shoulder [8]. The autonomic and motor symptoms that sometimes accompany this disease process can include nausea, vomiting, muscle tenderness, and sweating [8]. These are the autonomic and motor inputs that sometimes accompany visceral pain as alluded to previously. This applies to any visceral pain, not just chest pain. It is believed that transient ischemia increases afferent activity in sympathetic and parasympathetic fibers [8]. Secondarily, sensitization of receptors and inflammation may stimulate visceral pain signals [8]. Investigations become important at this stage in the diagnosis and treatment of this pain. A thorough history is an important non-invasive method of investigating for visceral chest pain of cardiac origin. This includes eliciting a family history of coronary artery disease and a personal history of hyperlipidemia, diabetes, and/or hypertension [9]. Features suggestive of cardiac visceral pain include a central substernal location and radiation to the left arm and shoulder or jaw [9]. Other important features include a tight, squeezing sensation, a duration of <5 min, worsening with exertion, and relief with nitrates [9]. Further investigations for cardiac origin of visceral pain should include a thorough physical exam, cardiac enzyme levels, resting ECG, and stress testing with echo or ECG [9]. More recently the use of cardiac MRI and CT imaging have shown promise for the future of diagnosing coronary artery disease as the cause of visceral chest pain [9].

Visceral esophageal pain may present similarly and it is important to be on the lookout for important clinical clues which may point toward this diagnosis over cardiac pain. Esophageal pain is usually accompanied by referral to the anterior chest wall as well as the back [8]. Accompanying autonomic symptoms can include nausea, sweating, secondary muscle contraction, and cutaneous hyperalgesia [8]. Mucosal irritation within the esophagus, most commonly caused by gastroesophageal reflux disease. Acid is believed to contribute to mechanoreceptor and chemoreceptor stimulation resulting in a pain pathway stimulus; similarly luminal distention may provoke these pathways through the stimulation of mechanoreceptors [8]. Pain from two different sources of thoracic viscera can be hard to differentiate clinically purely based on patient description. The heart and esophagus have overlapping visceral dermatomes [8]. In differentiating cardiac from non-cardiac chest pain, several sources are important to consider. These include esophageal, musculoskeletal, hyperventilation, and psychological [9]. In one study, the majority of patients with visceral chest pain admitted for cardiac care suffered from what is known as “true angina”, with 10–30% of them having no cardiac abnormality identified [8]. On follow-up, 35% had some form of heart disease while 58% had an esophageal disease process [8]. Once again, a thorough history is invaluable in differentiating some of these causes. Up to 10% of reflux sufferers present with chest pain as the only symptom; many otherwise healthy people may have silent reflux and present asymptomatically [8]. Once cardiac chest pain has been ruled out, other culprits may be investigated. The gold standard for investigating gastroesophageal reflux disease is 24-hour pH monitoring; Esophageal manometry may also be considered to rule out any motility disorder [8]. Psychiatric referral and evaluation may elicit any psychogenic causes once other more organic causes have been ruled out [8].

Visceral abdominal and pelvic pain will present in a similar fashion to visceral chest pain, however the anatomy differs quite a bit. As with all other forms of visceral pain, it presents as poorly defined or diffuse [5]. In contrast, a sharp, well localized pain may indicated peritoneal irritation rather than disease limited to the viscera [10]. Similarly to any other presentation of pain, evaluation may begin with a thorough history eliciting aspects such as location, quality, radiation, severity, and temporal qualities [10]. Diagnosing abdominal visceral pain lends itself to a thorough knowledge of embryology. Pain from the embryologic foregut will typically localize to the epigastric region; this includes the stomach, proximal duodenum, pancreas, liver, and biliary tree [10]. The remaining small bowel and proximal one-third of the colon along with the appendix will typically refer to the periumbilical region as these are midgut structures [10]. Finally, hindgut derived organs such as the bladder and distal two-thirds of the colon as well as the genitourinary structures of the pelvis will cause pain in the suprapubic region [10]. Beyond location, characteristics of the pain can be used to form a more narrow differential. Acute onset, for example should always prompt investigation for a more sinister cause such as a ruptured abdominal aortic aneurysm or a bowel perforation [10]. In contrast, gradual processes such as infection or inflammation will more commonly present with a gradual onset of pain [10]. Associated symptoms such as nausea, vomiting, and diaphoresis may also be seen with abdominal or pelvic visceral pain, due once again to stimulation of autonomic and motor fibers [5]. Physical exam should be performed with inspection, auscultation, palpation, and percussion. The testing for localized tenderness or guarding can indicate peritoneal irritation [10].

In conducting investigations for visceral abdominal and pelvic pain, it is important to realize that there are limitations to many forms of imaging and lab studies. Therefore, a thorough history and physical that presents a high pre-test probability of the disease should not be discounted in favor of positive imaging or lab results [10]. The initial workup of abdominal and pelvic pain should include several lab measurements. Most patients should receive a complete blood count with differential, a complete metabolic panel, calcium levels, liver function tests, measurement of lipase and/or amylase, iron studies, and possibly anti-tissue transglutaminase titers [11]. Special patient populations warrant further initial testing. For example, women of child bearing age should receive a pregnancy screening and immunocompromised patients presenting with abdominal or pelvic pain may warrant screening for opportunistic infections [11]. In older patients, an acute abdominal or pelvic process may not present in the same way as younger patients, they may not present with fever or abnormal lab values quite as quickly or as often, this is important to keep in mind as an acute abdomen in older patients may carry a mortality as high as 14% [10]. The unstable patient requires resuscitation whereas stability warrants further investigation which may come in the form of abdominal imaging such as a CT scan or abdominal radiographs [10]. These imaging studies also carry limitations however; for example, upright plain films will miss free air in up to 40% of patients with a perforated viscus [10]. Further imaging and lab tests depend on the differential at hand and may include more invasive techniques such as ERCP, cholangiograms, colonoscopies, etc. [11] The goal of each of these investigative studies

is to diagnose and treat. Treatment of visceral pain has evolved tremendously throughout the years and the remainder of this chapter will focus on both well-established and newer modalities of pain management.

39.4 Treatment

The following discussion of the treatment of visceral, organ-related pain will be broken down into several categories. These include non-pharmacological management, pharmacological management, interventions, and new modalities. Each of these treatments has advantages and disadvantages and some patients may respond appropriately to one and not the other. Regardless, these all represent viable options in the management of the inpatient with visceral pain. Opioids, Non-steroidal anti-inflammatory drugs, serotonergic, and other miscellaneous analgesics form the vast array of pharmaceutical options at the clinician's disposal in treating visceral pain [5]. However, treatment goes beyond distributing pharmaceuticals and a host of viable alternatives exist.

Non-pharmacological management exists in many forms. Behavioral modalities are but one of these forms of treatment. Psychological distress has been shown to provoke or exacerbate chronic pain symptoms [12]. Several studies have examined the role of psychological intervention in the treatment of chronic pain. One meta-analysis found an overall benefit in symptoms of chronic abdominal pain in patient with irritable bowel syndrome when targeting psychological symptoms such as anxiety and depression [12]. Hypnotherapy was one modality observed in this study. Cognitive behavioral therapy (CBT) has also shown tremendous promise as a form of non-pharmacological treatment of chronic abdominal pain. Visceral pain has been linked with increased limbic system activity in the brain; one study has shown that CBT is associated with changes in the neuronal activity of the cingulate gyrus, a key component of the limbic system [12]. The difference between CBT and educational therapy has also been examined in terms of the limitations of each. One study showed that CBT was superior to educational therapy in that 70% of patients saw a benefit as opposed to 37% who only received education [12].

Spinal manipulation in the form of physical medicine has long been seen as a viable option for treating biomechanical disorders associated with musculoskeletal pathology [13]. Its usefulness in the treatment of non-musculoskeletal disease remains a debated topic; the argument against it is that there is no established neurobiological mechanism by which it could help the patient with visceral pain; regardless research into its potential continues [13]. Very few patients receive spinal manipulation for non-musculoskeletal pain in the modern era. In one Danish study, patients presenting to chiropractors for non-musculoskeletal pain fell from 7 to 3% [13]. Despite this, there have been some promising results in the literature. Visceral responses to spinal manipulation have been documented in several studies. Cardiovascular parameters such as heart rate, blood pressure, and heart rate variability have been shown to change dramatically during the course of spinal

manipulation therapy [13]. Similarly, the effect of spinal manipulation on respiratory and gastrointestinal function have been well documented [13]. It is clear that spinal manipulation involves the visceral pathway in one form or another, even going so far as regulating immune function [13]. In several studies, spinal manipulation therapy was associated with increased immune function as observed via increased chemiluminescence in immune cells and increased production of compounds such as substance P and tumor necrosis factor [13]. The clinical efficacy of spinal manipulation therapy may therefore seem somewhat plausible however further research on the matter may elucidate its utility further.

Other novel approaches in the non-pharmacological treatment of organ-related pain have been shown to be effective. In a Dutch study, yoga exercises resulted in significant reduction of pain in children with gastrointestinal disease [14]. Similar benefits have been documented in other populations as well [14]. Acupuncture has also shown some benefits in various studies. A study comprised of adult participants compared the beneficial effects of acupuncture and more traditional western medications; acupuncture was shown to be superior in its relief of symptoms [14]. The benefit of acupuncture in treating pain is believed to be due to its effects on the release of endogenous opioids and its effect on serotoninergic inhibitory pathways in the nervous system [14]. Of course, behavioral changes can always be another important aspect of non-pharmacological management in those with organ-related visceral pain. This can be anything from cessation of alcohol in those with pancreatic disease to abstaining from fatty foods in those predisposed to gallstones. The selection of non-pharmacological management will depend on the patient and the presentation.

The pharmacological management of visceral organ-related pain can be a book in and of itself. Here we will discuss the most common options as well as some adjuvant modalities. This is not an exhaustive list but rather an overview of some of the more common analgesic options.

Non-steroidal anti-inflammatory drugs (NSAIDs) are some of the most common medications used on a daily basis for pain management. NSAIDs are not selective for visceral pain however and are also used to treat other forms of chronic pain [5]. In some cases, NSAIDs have shown mixed results in suppressing visceral pain in some models. In one study conducted in rats, several NSAIDs had shown minimal analgesia in test subjects. At the same time, higher doses had shown marked pain-relief [15]. The data in this particular experiment showed that rather than the classical prostaglandin inhibiting effects of NSAIDs, it is an alternative visceral pathway that higher doses may effect that causes the analgesic effects [15]. In another study, visceral pain response to standard opioids and steroids as well as NSAIDs was assessed, also in a visceral rat model. It was concluded that NSAIDs reduced pain behavior and inflammatory responses, but there was minimal effect on referred hyperalgesia [16]. NSAIDs remain one of the most widely used over the counter drugs in the world. For this reason, it is important to educate patients on some of the side effects of NSAIDs. These include gastrointestinal ulcers, platelet dysfunction, nephrotoxicity, and hypersensitivity reactions [17]. This is important when dealing with patient populations with relevant comorbidities such as chronic kidney disease

or gastrointestinal diseases. In order to avoid some of the gastrointestinal side effects, some patients in which NSAIDs should generally be limited are those over the age of 65, those receiving hemodialysis, patients with Helicobacter pylori colonization, patients on anticoagulants, patients on SSRIs, and in some cases patients using alcohol or tobacco [17]. Similarly cardiovascular side effects can be avoided by limiting NSAID use in patients with unstable angina or myocardial infarction, recent cardiac bypass surgery or coronary stent placement, patients with hypertension, and patients with heart failure [17].

Acetaminophen (or paracetamol) is an option that can be considered if trying to avoid the myriad of adverse effects associated with NSAIDs. It is an analgesic and antipyretic, and differs from NSAIDs in that it has a weak anti-inflammatory effect [17]. In animal models, acetaminophen has been shown to be an effective adjunct to opioids in the treatment of visceral pain [18]. A 2011 study utilizing mouse models showed a synergistic inhibitory nociceptive effect when combining fentanyl, acetaminophen and trazodone [18]. It was hypothesized that endogenous opioids may have played a significant role in these analgesic effects [18]. In 2010, the FDA approved OFIRMEV, an intravenous form of acetaminophen which has found widespread use in the treatment of mild to moderate pain as well as severe pain in conjunction with opioid analgesics [17]. This form of acetaminophen has found its way into surgery centers throughout the country serving as an effective option for inpatients recovering from surgery [17]. Indeed, acetaminophen has shown tremendous potential for treating visceral pain when combined with other analgesics. Acetaminophen is regarded as possibly the safest and most cost-effective non-opioid analgesic when dosed at analgesic levels [17]. Acetaminophen is therefore a very viable option for the inpatient with visceral pain.

Opioids remain one of the most reliable forms of analgesics when treating chronic visceral pain conditions, however they can sometimes be limited by their side-effects [5]. There are several scenarios in which opioids become preferable to NSAIDs. Patients with hematologic complications should avoid the platelet dysfunction that may accompany NSAID use, therefore opioids may be the better option [19]. Similarly, patients with renal disease, liver dysfunction, history of peptic ulcers or esophagitis, and pregnant women may be better candidates for opioid based therapies rather than NSAIDs [19]. There is little evidence supporting long-term use of opioids in treating chronic non-cancer pain however [20]. This is particularly due to the side effect profile of long-term opioid use. In one meta-analysis, a clinical trial investigating the effects of long-term opioid use for chronic pain was analyzed; oral opioids were discontinued in 23% of patients due to side effects [20]. Another 10% were lost due to inadequate analgesia. At the end of the study, 58% of the original participants remained [20]. The meta-analysis demonstrated insufficient evidence for an improvement in the function or quality of life of patients [20]. Furthermore, it has been demonstrated that around 80% of patients using opioids experience at least one side effect; this is most commonly constipation, nausea, vomiting, or sedation [20]. The relatively widespread incidence of these effects should therefore spark caution in clinicians when prescribing opioids for visceral pain, especially on a long term basis. Less common side effects of opioids include

pruritis, sweating, hypogonadism and bladder dysfunction [20]. The most serious side effects can include respiratory depression, hypotension, and coma [20]. Opioid tolerance and physical dependence also become an issue in chronic pain patients as dosages need to be increased to achieve the same analgesic effect over time [20]. It is important to note that randomized controlled trials have shown that the use of combined synergistic formulations which include opioids leads to superior pain relief when compared to opioids alone [19]. This "multimodal analgesia" involves the simultaneous occupation of different receptors to achieve pain relief and at the same time reduces the opioid dosage needed to achieve a given level of analgesia [19]. Regardless of their controversy, in the hands of an experienced clinician, opioids must remain an integral part of inpatient visceral pain management.

Anticonvulsants are another option for the treatment of visceral pain in the inpatient. Much research has been conducted about the role of anticonvulsants as both primary analgesics and as a part of synergistic formulations. Pain management after cardiac surgery is one domain in which anticonvulsants have recently made headway as viable analgesic options. Cardiac surgery may induce visceral, musculoskeletal, and neurogenic pain [21]. Pain control in these instances is achieved with multimodal regimens utilizing opioids, acetaminophen, NSAIDs, and now anticonvulsants [21]. There appears to be a plethora of data concerning anticonvulsants in the treatment of musculoskeletal, neuropathic, and inflammatory somatic pain; however, visceral pain is an avenue that, up until now, has not been equally represented in the literature [22]. In one study out of Serbia, animal models demonstrated significant dose-dependent reductions in quantified visceral pain impulses when given doses of anticonvulsants such as carbamazepine, oxcarbazepine, gabapentin, and topiramate; Topiramate was the most effective drug in this model [22]. Similarly, animal models have shown great promise for increased usage of anticonvulsants in a synergistic role. For example, paracetamol and oxcarbazepine have been shown to be particularly effective in these trials [23]. In the perioperative scenario, anticonvulsants may be of great use for analgesia of chronic visceral pain. Anticonvulsants should however be used mainly for neuropathic pain, as the evidence for visceral pain treatment is yet to be substantial [24]. It is important to note that long-term users of anticonvulsants may develop biochemical and hematological complications and it is advisable to track electrolytes and full blood counts periodically [24]. It is also advisable to avoid abrupt discontinuation of the medication as withdrawal symptoms can be common [24]. Systematic reviews of anticonvulsants in the inpatient arena, particularly perioperatively, have demonstrated reduced pain scores and lower opioid dose requirements making anticonvulsants analgesics to keep in mind [24].

There remain a tremendous amount of pharmacologic options for inpatient visceral pain not covered here. These are however some of the most common options one will find in the inpatient setting. In addition to those presented above, novel adjuvant medications such as cannabis and Botox have shown some promise in treating visceral pain [17]. Studies have shown that cannabinoids have tremendous potential in treating both neuropathic and non-neuropathic pain. Recent studies have demonstrated a relatively good safety profile, however larger studies must be

implemented before it can make its way into standard inpatient guidleines [17]. Botox has also been shown to be a theoretically sound adjunct for the treatment of visceral pain. The effect of analgesia is thought to be related to its effects on neurotransmitter and neuropeptide release [17]. Its role in visceral pain may lie in its ability to reduce TRPV1 and sodium channel activity as well as its inhibition of inflammatory processes at nerve terminals [17]. The future of adjuvant treatments does appear to be a bright one.

Further interventions in the treatment of inpatient visceral pain may go beyond primary non-pharmacological and pharmacological, and instead require more invasive techniques. In many cases, medical management with opioids and other analgesics may not be enough to control pain.

Sympathetic nerve blocks have been used for the treatment of visceral pain for many years. For instance, the World Health Organization has recommended the use of NSAIDs, opioids, and other adjuvant analgesics for visceral cancer pain relief [25]. Some studies examining visceral pain relief have called this recommendation into question however. In one Brazilian study comparing traditional medical management with sympathetic nerve blocks, patients were divided into experimental groups, some receiving medical management alone, some receiving some combination of sympathetic nerve blocks [25]. Groups receiving medical management alone had lower levels of pain relief, higher opioid consumption, and more abundant adverse effects [25]. The sympathetic nerve block groups reported greater reduction in pain, less opioid consumption, and only relatively minor adverse effects as a result of the sympathetic blocks [25]. A systematic review conducted in 2014 compiled evidence for the benefit of sympathetic blocks in adult cancer patients with abdominal visceral pain. The review showed that different variations of sympathetic blocks provided adequate analgesia in most patients, while at the same time reducing opioid consumption [26]. For these reasons, sympathetic blocks appear to be a viable alternative in patients with either refractory visceral pain or risk of opioid dependence.

Neuraxial analgesia is another intervention that can be performed in patients with visceral organ pain. This is done via an epidural or intrathecal route. The decision in which route to administer the analgesic has to do with both the location and the mechanism of pain [27]. Patients with cancer-related visceral pain who have a longer life expectancy can benefit from an implanted neuraxial system which dispenses the analgesic [27]. Several studies have shown a benefit of neuraxial analgesia in select patients however these also noted some severe side effects to neuraxial analgesia in fragile patients [27]. This may manifest as trauma to the spinal cord or it's fibers, headaches after puncture of the dura, epidural hematomas, infections, catheter migration, and others [27]. For these reasons, candidates for neuraxial analgesia should be carefully selected based on patient demographic and comorbidity.

Several other more advanced and minimally invasive techniques exist for the treatment of cancer-related pain as well as visceral pain in general. These include percutaneous vertebroplasty, kyphoplasty, radiofrequency ablation, and cryoablation [27]. However, these are limited largely by the shortage of trained practitioners that are able to perform them. Therefore, current recommendations are for these

options to be reserved for select patients with severe and disabling visceral pain refractory to other analgesic treatments [27]. Spinal cord stimulation has also shown some promise in treating the visceral components of pain. Several case reports have shown the use of spinal column stimulation in the treatment of visceral pain syndromes, such as those found in cases of ulcerative colitis and Crohn's disease [28]. In these cases, spinal levels are chosen for stimulation based on the viscerotomal innervation they supply. For example, T5–6 will cover pancreatic pain whereas T6–7 may cover splenic pain [28]. There is promising potential in many of these techniques and they should become more and more widespread as research intensifies over the coming years.

New modalities in the pharmacological realm of visceral pain treatment have been explored in recent years. Visceral nociceptive pathways can be attacked from a number of angles so to speak, and some of the new modalities to come take advantage of this fact. Recent research studies have looked into the use of sodium channels and TRP channels as targets [29]. Activation of these TRP receptors is directly attributable to tissue injury or bacterial toxins, newer pharmacologic agents aim to block these receptors and thereby reduce subsequent neuropeptide release and inflammation at visceral afferents [29]. Similarly, sodium channel targets have been the basis of research due to their effects on visceral afferent input [5]. The neuromodulation of these targets is a hot topic in the current research towards visceral pain management.

39.5 Pain Assessment Tools

Pain can be a very subjective topic on the wards. For this reason, pain assessment is an invaluable skill at the clinician's disposal. Several aspects can define a patient's pain. These include pain severity, chronicity, and pain experience which itself encompasses pain intensity and pain affect [30]. The visual analogue scale is one method of quantifying pain. This entails using a visual aid such as a straight line with an end on each side. The patient can then pick a point on the line that they believe best describes their current pain [30]. This line can also be customized with descriptors such as mild, moderate, or severe [30]. This method of pain assessment has been criticized for its tendency toward misinterpretation, especially in elderly patients [30]. Another method of pain assessment is the numerical rating scale. This is what is usually seen on the hospital floor. A patient will pick a number from 0 to 10 that best describes their current pain level [30]. This method has been applauded for its ease of use and ability to be administered verbally, key for phone interviews. In the inpatient setting, it has demonstrated good ease of use and good patient compliance [30]. Pain drawing is another method that can be utilized. The patient is provided a drawing of a human figure and asked to mark on the figure where they feel pain the most. Some forms of this assessment tool will ask the patient to just mark a location whereas others delve deeper and ask for the patient's description of the pain via symbols that may indicate qualities such as burning or electrifying [30].

The disadvantage of this method lies in the inability to administer this verbally. In addition, studies have demonstrated that this method was unable to predict outcomes of surgical and non-surgical management of chronic lower back pain, therefore its use for other forms of pain may also be limited [30]. With the verbal rating scale, adjectives describe pain levels. Two extremes are generally outlined such as "no pain at all" and "extremely intense pain" [30]. The patient is then asked to choose from either these extremes or listed adjectives which bridge the gap. A disadvantage of this method is that it can be time consuming [30]. It also presents subjective values for the patient to choose from [30]. What might be "extremely intense pain" for one patient may not be so for another.

Several instruments have also been devised to measure pain levels. The Pain-O-Meter consists of two lists of terms. Each term has an intensity level that is given a value of one to five. The patient will then assign a number to each term and once these values are added up, the clinician is provided a Pain-O-Meter-affective scale [30]. This tool has been shown to be very reliable and sensitive in various hospital settings [30]. Finally, the McGill Pain Questionnaire (MPQ) is a tool that has seen some use in the inpatient setting. The questionnaire consists of three measures: pain-rating index, number of words chosen to describe the pain, and present pain intensity on a scale of one through five [30]. It has been described as the most extensive tool measuring pain affect and its utility has been demonstrated in many studies [30].

39.6 Challenges in Management of Pain While in the Hospital

The challenges in management of pain while in the hospital can fill a textbook on its own. As has been outlined in this chapter, there are a myriad of complexities and intricacies that one must be aware of when planning for pain management in the inpatient. The mismanagement or undermanagement of acute pain can lead the way to chronic pain and chronic pain leads the way toward psychological and social issues [31]. Various physical and psychological effects are associated with the undertreatment of acute pain. These include but are not limited to increased metabolic demands, muscle breakdown, impaired limb movements which may lead to thromboembolisms, inhibition of gastrointestinal motility, and impaired immune response. In addition psychosocial factors of untreated acute pain must be considered [31]. As previously mentioned, the use of opioids may be widespread however their side effect profile presents a dilemma in using them consistently [20]. Similarly, other analgesics have shown side effect profiles which limit their long term use such as NSAIDs. Therefore, a balance between adequate treatment and limitation of side effects may be a considerable challenge in the inpatient setting. It becomes important in the inpatient setting to accurately judge the level of a patient's pain [31]. Clinicians must always be wary of drug-seeking behavior even in the inpatient setting. Tolerance and dependence are important aspects of drug treatment that must be

kept in mind. For example, slow-release opioids have been shown to have less addiction potential [31]. Some common warning signs of drug abuse in the inpatient setting may include refusal to taper medications, reports of only specific drugs working, strong preference for short-acting formulations, and use of multiple prescribing providers in the past [31].

Finally, as alluded to earlier, a patient's comorbidities will always dictate what medications may be used. For example, the patient with acute on chronic kidney disease with abdominal distention pain secondary to fluid overload will not do well on an NSAID [17]. Similarly, patients with gastrointestinal disease causing constipation-related pain should not be receiving opioids under any circumstances [20]. In many other patient populations, pain management can be extremely difficult. For example, obese patients may have difficulty tolerating opioids given their predisposition to sleep apnea and respiratory depression [32]. The consensus in this population has been to utilize a multimodal approach and avoid sedatives. Obese individuals receiving postoperative pain control required significantly smaller doses of opioids when utilizing a multimodal approach [32]. Chronic pain patients also pose an interesting subset of patients in this regard. For example, patients on chronic opioid use will require higher doses to achieve similar analgesic effects. This patient population also benefits from multimodal analgesia or continuous patient-controlled analgesia [32]. This group also benefits from long-acting opioid formulations [32]. The risks and benefits must always be weighed when formulating a pain treatment plan for the inpatient. Usually, a multimodal drug approach will have the best results in most inpatients with chronic pain [31]. A treatment plan should be initiated upon agreement with the patient and all parties involved, and said treatment plan should combine evidence-based medical practice with sound patient compliance [31].

39.7 Management of Pain in the Inpatient Setting

When formulating the treatment plan for the inpatient with visceral organ-related pain, there are many treatment medications and modalities to choose from. As outlined earlier, there are advantages and disadvantages to each of these and the treatment option of choice should be supported by clinical evidence-based medicine and input from both the patient and the rest of the treatment team. Mild to moderate pain should be treated with non-opioid pharmacologic agents. these include NSAIDs and acetaminophen [17]. The use of only one medication from an analgesic category is always recommended (i.e.; one NSAID instead of two or one opioid instead of two) [31]. For moderate to severe visceral pain, short term opioid treatment can be beneficial, however multimodal approaches have become the standard amongst practitioners based on evidence [19]. The general rule of thumb is to administer several drugs if and only if they work by different mechanisms [31]. For example, an NSAID, opioids, and acetaminophen may be used in conjunction in the treatment of acute or chronic pain. Interventional techniques have also become quite useful in the setting of inpatient visceral pain as evidenced by the success of techniques

such as neuraxial analgesia and sympathetic nerve blocks. These should remain in the arsenal of pain management options when patients are refractory to more conservative methods. In fact, prior to any pharmacological or invasive intervention, conservative approaches should always be exhaustive. Physical therapy, cognitive behavioral therapy, yoga, acupuncture, and other forms of conservative traditional pain management techniques all have their place. Some of these may not be available in the inpatient setting and it is up to the treatment team formulating the pain management plan to know when and where each modality has its place. What is important to consider for the astute clinician treating visceral, organ related pain is when to escalate to more pharmacological and invasive based techniques in order to limit any consequences of untreated pain in their patient.

39.8 Discharge Plan for Pain Management

Once the inpatient with visceral organ-related pain is discharged, adequate follow up becomes an important modality in and of itself. The lack of optimal discharge plans for outpatient treatment is may lead to refractory pain and the use of nonprescribed medications [33]. It is important to have a plan in place when the patient is discharged. This includes periodic follow up and assessment. Patients should be seen every 3 months after discharge in order to reassess the treatment plan and its efficacy [31]. Consultation with a pain specialist is an option in certain scenarios. Some of the more common reasons for referral to a pain specialist include debilitating symptoms, symptoms in multiple sites, refractory symptoms, and a need for increasing doses of medications [34]. If patients are prescribed outpatient treatment with medications that have long term consequences with chronic use, it is important to follow up more periodically in order to reassess the patient and their regimen and investigate for any side effects of the treatment. As discussed earlier, patient in need of long term pain relief should be counseled on the dangers of certain long term treatments such as opioids and NSAIDs. This is especially important in patients with relevant comorbidities. With a logical and well planned outpatient regimen, the patient's pain relief can be maximized.

39.9 Summary

- Workup of the inpatient with visceral organ related pain must begin with a thorough history and physical exam.
- Investigations including imaging and labs should be performed based on the acuity of the situation.
- Patients receiving treatment should be aware of all benefits, alternatives, and risks to which ever treatment modality is being considered. The goals of treatment should be reviewed with the patient.

- The treatment plan should be discussed with the entire treatment team and should be based on sound evidence-based data and established clinical practice.
- Conservative non-pharmacological treatment options should be the forefront of any treatment plan.
- Pharmacological management choice should be based on patient preference, comorbidities, availability, cost, and side effect profile.
- More invasive techniques should only be considered in patients whose pain is refractory to more conservative measures.
- Adequate pain assessment is an important tool when deciding on treatment modality and treatment necessity.
- The patient with chronic visceral pain receiving treatment should always be re-evaluated and treatment adjusted accordingly.

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Chapter 40
Management of Small and Large Bowel Obstructions

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40.1 Introduction

Small and large bowel obstructions are some of the most common causes of abdominal pain in the world, with approximately 15% of all admissions for abdominal pain being secondary to small bowel obstruction. About 300,000 people are diagnosed with small bowel obstruction annually [1]. While rarer, large bowel obstruction tend to be more damaging, often leading to a worse overall prognosis and outcome. Although treatment regimens for the disease process have been well discussed and protocoled, treatment of underlying pain can be challenging in these patients. Opioids have long been the mainstay of treatment, but often lead to more deleterious outcomes such as further worsening of their obstructive symptoms. More interventional, opioid free treatment options, including TAP blocks and catheters, and epidurals are slowly becoming the new standard of care. In this chapter, we will discuss the signs and symptoms of small and large bowel obstruction, the appropriate steps to take to ensure correctly diagnosing these patients, and finally discussing both new and old treatment options for their acute and chronic pain.

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40.2 Type of Population

Both large and small bowel obstructions occur in similar incidences between men and women. Small bowel obstructions are more common in patients who have a history of multiple surgical procedures, as the most common cause of small bowel obstruction is adhesions [1]. Large bowel obstructions most commonly occur in patients with a history of malignancy, followed by patients with diverticular disease causing stricture [2–4]. Thus, patient's with such history as colon cancer or Crohn's disease and ulcerative colitis are more prone to large bowel obstruction.

40.3 Types of Disease and Causes of Obstruction

There are two types of obstruction, small and large bowel obstructions. The cause of obstruction can vary for the different forms. For small bowel obstructions, the most common cause of obstruction is an intra-abdominal adhesion secondary to prior surgeries [1]. This can lead to physical stenosis of the small bowel causing the inability of food contents to be advanced through the GI tract with peristalsis. Other causes include hernias, malignancy, inflammatory bowel disease (Crohn's disease) and the presence of volvulus [1]. Regardless of the etiology, the pathophysiology remains consistent among all these disease processes. Specifically, luminal narrowing of the small bowel leads to proximal dilatation of the intestine secondary to accumulation of GI secretions, and swallowed air. This in turn stimulates cell secretory activity, resulting in further fluid accumulation. Increased peristalsis can lead to increased gut motility distal to the obstruction, so frequent loose stools early on in the disease course are not uncommon. As bowel dilatation continues, transluminal pressure exceeds capillary bed pressure, leading to hemostasis, and absence of forward blood flow to the intestine. If continued, this can lead to ischemia of the bowel, weakening of the bowel wall, eventual perforation, and translocation of bacteria into the peritoneal cavity [1].

Large bowel obstructions are most often secondary to a GI malignancy, followed by diverticular disease, colonic volvulus, intussusception and stool impaction/obstipation [2–4]. They follow the same pathophysiologic course as small bowel obstruction but are secondary to different predisposing conditions. A unique syndrome seen only with pseudo obstruction of the large bowel is called acute colonic pseudo—obstruction, or Ogilivie syndrome. In this syndrome, which has many etiologies, a functional obstruction occurs without any mechanical blockage. It is typically seen in elderly or debilitated patients, and is thought to occur secondary to a decreased parasympathetic or excessive sympathetic tone in these patients [5]. In a retrospective review of more than 1400 patients with ACPO, the most common causes included operative and non-operative trauma (11%), infections (10%), and cardiac disease (10–18%) [6, 7].

40.4 Medical Problems

Medical problems associated with bowel obstruction include any problem that can occur with malfunction of the GI tract. For small bowel obstructions, this includes extreme nausea, with bilious emesis, poor appetite, poor absorption of nutrients, weight loss, and malnutrition. Furthermore, multiple episodes of emesis can lead to irritation of the GI tract, causing an upper GI bleed, leading to anemia. Aspiration is also a risk encountered with small bowel obstruction as patients with multiple episodes of emesis and poor nutrition can have profound lethargy, leading to higher rates of aspiration, and complications arising from this. For patients with large bowel obstruction, constipation is the most frequent complaint that brings patients to the emergency department. More serious medical problems include metastatic malignancy causing hepatic and other organ dysfunction, bowel ischemia, and perforation proximal to the level of obstruction from bowel dilation.

40.5 Coexisting Medical Conditions

As previously stated, the most common cause of small bowel obstruction is intra-abdominal adhesions from prior surgeries. Examples of the most common surgeries include cholecystectomy, partial small bowel resections secondary to inflammatory bowel disease, and appendectomies. Other medical conditions predisposing to small bowel obstruction include presence of umbilical and inguinal hernias, as well as an intra-abdominal malignancy (ex. hepatocellular carcinoma, pancreatic cancer, renal cell carcinoma, etc.)

For large bowel obstructions, the most common co existing medical conditions include colon cancer, and Crohn's disease/Ulcerative colitis. These medical conditions can lead patients having either a physical obstruction (large mass in the setting of colon cancer), or colon narrowing secondary to inflammation and stricturing of the GI tract (Crohn's disease and ulcerative colitis).

40.6 Pathophysiology of Bowel Obstruction

40.6.1 Arterial Supply and Innervation

The small bowel begins with the first portion of the duodenum and terminates at the ileocecal valve. Consisting of approximately 20 ft of tissue, the small intestine is supplied by the gastroduodenal artery via the superior anterior and posterior pancreaticoduodenal arteries, and branches of the superior mesenteric artery (including the inferior and posterior pancreaticoduodenal arteries, and the jejunal and ileal

arteries) [8, 9]. There are two types of nerve fibers that innervate the entirety of the small bowel, the parasympathetic and the sympathetic nerve fibers. The sympathetic nerve fibers to the small bowel originate in the paravertebral thoracic sympathetic trunk, traveling to the celiac and superior mesenteric ganglia, and then eventually innervating the length of the small intestine. After synapsing at the celiac and superior mesenteric ganglia, they are known as the greater and lesser splanchnic nerves, respectively. They provide a "brake system" to the bowels, specifically stopping peristalsis in times of heightened sympathetic activity in the body. The parasympathetic fibers to the small intestine originate from the vagus nerve, and travel to both the celiac and superior mesenteric ganglia, eventually innervating the duodenum, as well as synapsing in the myenteric and submucosal plexuses of the intestinal wall, and providing parasympathetic activity to the jejunum and ileum [9].

The large bowel consists of the cecum, ascending colon, transverse colon, descending colon, and the sigmoid colon. Its arterial supply is predominantly by branches of the superior mesenteric and inferior mesenteric arteries. The superior mesenteric artery and its branches supply the mid gut, from cecum to the proximal two-thirds of the transverse colon, while the inferior mesenteric artery supplies the hindgut, from the distal one-third of the transverse colon to the end of the sigmoid colon. Innervation of the large intestine is also supplied via parasympathetic and sympathetic nerve fibers. The vagus nerve travels to the large intestine to provide parasympathetic innervation, in conjunction with the pelvic splanchnic nerves that originate at S2–S4 in the spinal cord. Sympathetic innervation to the large intestine originates at the T10–L2 thoracolumbar paravertebral sympathetic chain with synapses at the superior and inferior mesenteric, and inferior hypogastric plexuses. The superior mesenteric pleuxus provides sympathetic innervation to the cecum, appendix, and the ascending and transverse colon, while the inferior mesenteric plexus innervates the colon from the splenic flexure to the rectum. The inferior hypogastric plexus innervates the rectum [10]. It is these nerve fibers that can be blocked by several regional anesthetic techniques discussed later that can provide resolution of bowel obstruction.

40.6.2 Clinical Features

For small bowel obstruction, certain key signs and symptoms will help to narrow in the diagnosis. Firstly, the patient will often complain of food intolerance, and severe nausea. Associated with nausea, the patient may also complain of multiple episodes of bilious emesis. A prior medical history of intra-abdominal surgeries is another feature seen in small bowel obstructions. Physical exam will be pertinent for a patient in moderate to severe distress, with active retching or emetic episodes during the exam. Abdominal exam features that are concerning for small bowel obstruction include distended abdomen, with mild guarding but with no rebound tenderness. Auscultation of the abdomen will reveal hyperactive, or tinkling, bowel sounds. Percussion of the abdomen will reveal a tympanic sound, signifying large volumes of air in the abdomen.

Large bowel obstructions are harder to clinically diagnose. Far and away, the most common chief complaint for patients with large bowel obstruction is constipation. Other symptoms will include food intolerance, weight loss, nausea, and B symptoms such as night sweats, fever, and chills. These are more concerning for a malignancy. Patients with a prior history of Crohn's disease, ulcerative colitis, or intra-abdominal malignancy are also key features for patients who present with large bowel obstruction. Physical exam may not reveal any abnormalities but patients presenting with a distended abdomen may be more likely in the setting of prolonged obstruction.

40.6.3 Lab Testing

Relevant blood work should be obtained to further aid in confirming the diagnosis, including complete blood count, and a complete metabolic profile. Lactate levels should also be ordered to determine if there is ongoing bowel ischemia. Finally, relevant imaging should be acquired as soon as possible. Abdominal plain film x-rays should be ordered first, and at least two views, both supine and upright are required. Even with this, a 30% diagnostic failure rate has been reported [11]. The imaging modality of choice presently is a CT scan of the abdomen. One study looking at the efficacy of CT scans showed a 94% sensitivity and 71% specificity rate, thus allowing physicians to confidently rule out obstructions, both large and small, if imaging is negative. A more accurate test, if clinical signs of obstruction are present but imaging is negative includes a CT enterogram, where thin slices of the bowel are obtained while drinking large volumes of contrast. This imaging modality has been more accurate than conventional CT scans in determining the cause of obstruction, as well as the location of the site of obstruction. If large bowel obstruction is suspected, retrograde contrast can be administered while obtaining plain film x-rays and CT scans to determine location of obstruction. A less sensitive, but more specific and quicker imaging modality that has recently been used to identify obstruction is the abdominal ultrasound, which in one study, had a reported specificity of 84% for SBO [12] (Figs. 40.1 and 40.2).

40.7 Pain Evaluation

40.7.1 Look for Completion of Workup by Primary Service

Prior to being consulted as the pain physician for a patient with bowel obstruction, it is important to ensure the primary service has accurately diagnosed and appropriately managed the condition. This includes, as described above, obtaining relevant lab work and imaging to confirm the diagnosis, and managed any operative intervention that may be required.

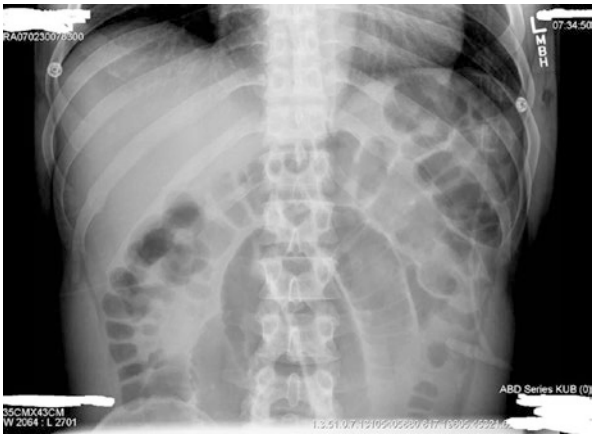

Fig. 40.1 Dilated loops of small bowel consistent with small bowel obstruction on plain film x-ray [1]

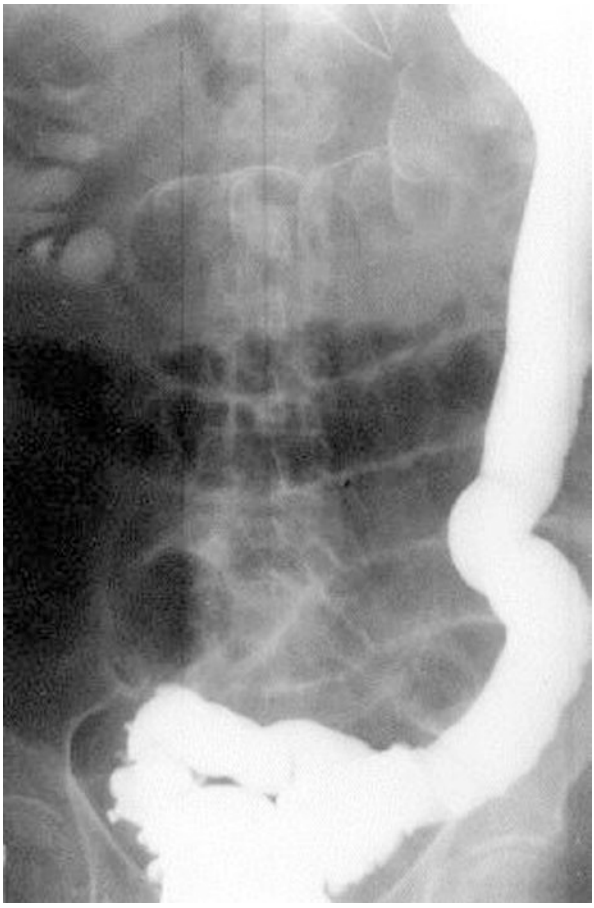

Fig. 40.2 Retrograde administration of contrast and plain film abdominal x-ray showing large bowel obstruction at the level of the splenic flexure [13]

40.7.2 Problems of Pain Evaluation in Elderly/Confused Patients

As patients undergo a hospital admission, signs/symptoms of delirium may present, and it is up to the provider to be able to detect a possibly confused patient to be able to assess them appropriately. If encountering an altered patient, whether chronic or acute, it is best to alter your practice to assess their true pain rating. According to Brown, rather than asking a numerical pain score in confused patients, it is necessary to consider a broader approach to pain assessment. This includes six areas that should be included in the assessment: facial expression, negative vocalization (or the lack of being able to speak secondary to pain), body language, changes in activity patterns or routine, changes in interpersonal interactions, and lastly recent mental status changes. The same assessment technique should be used in the elderly who are similarly unable to vocalize pain scores. The Abbey Pain Scale is a pain assessment tool that was designed initially for patients with late stage dementia, but can also be useful in acutely altered, or the elderly patients [14].

40.7.3 OR or No OR

Small bowel obstructions are managed in two predominant manners. They are managed with either medical therapy, or surgical intervention. Medical management can commence when the following criteria are met:

1. Absence of strangulation on imaging (CT scan of the abdomen).
2. Absence of history of persistent, metabolite altering emesis.
3. Malignant metastatic tumor is the cause of obstruction—in this case, medical management should be chosen first, and patients should be reverted to surgical therapy only if required for palliative purposes.
4. Cause of obstruction is secondary to inflammatory bowel disease: treatment should include high dose steroids, nasogastric tube decompression, and parenteral treatment for prolonged periods of time.
5. Intra-abdominal abscess—CT guided abscess drainage should be initial treatment of choice.
6. Radiation enteritis—treatment should commence with high dose steroids to reduce post radiation swelling if acute. If the disease process is chronic in nature, consider surgical correction.
7. Incarcerated but NOT strangulated hernia—manual reduction and observation is recommended first, along with scheduling the patient for elective hernia repair after the acute disease process is over.
8. Adhesions as the causative agent for SBO—consider avoiding further surgery as it can propagate the problem of small bowel obstruction in the future.

If these criteria are not met, then the patient is typically prepped for surgery, as operative intervention is the key management. For patients with large bowel obstruction, the most common cause is colonic malignancy. In these patients, the decision may be made to operate for palliative purposes. Otherwise, medical management with proper bowel regimen, and adequate pain control is the mainstay of therapy. For patients with other causes of large bowel obstruction, such as inflammatory bowel disease, the primary service may decide to operate with procedures such as total abdominal colectomy being part of the treatment plan. It is the job of the pain physician to acknowledge the type of treatment plan that is decided upon by the primary service, either operative or non-operative, and to formulate a pain control regimen suited for that patient.

40.7.4 NPO Status

It is important to be aware of your patient's NPO status as this can change the treatment plan significantly. Often the best mode of treatment for patients who are able to tolerate a PO diet is multimodal in nature. However, in patients with bowel obstruction, the ability to tolerate PO is often limited, and thus patients are usually put on an NPO status. This prevents their ability to utilize some medications that may otherwise be helpful such as gabapentin, Tylenol, NSAIDs, and Tramadol, which all act on different receptors to help alleviate pain. In patients who are NPO, it is best to consider alternate form of pain management such as IV pain medications, topical local anesthetic patches, and interventional pain management techniques.

40.7.5 Coagulopathy

Coagulopathies can play a major role in interventional pain management techniques. While there are many reasons for patients to become coagulopathic, in the setting of bowel obstruction, the key reasons to be aware of include intra hepatic malignancy destroying the body's ability to generate coagulation factors, and postoperative coagulopathy secondary to large volume blood loss anemia and inadequate resuscitation. Similarly, as patients may be coagulopathic at baseline, they may also be coagulopathic secondary to in hospital anticoagulation. It is important to recognize patients who are on anticoagulation as treatment options may change or be limited in these settings. The American Society of Regional Anesthesia has a consensus guideline for patients on different types of anticoagulation and the appropriate time to wait prior to performing an interventional procedure such as a nerve block or epidural catheter placement [15].

40.7.6 Previous Surgeries, Spinal Deformities, and Distorted Anatomy

The presence of a prior surgical history is of the utmost importance when considering interventional pain management techniques. For instance, patients with a history of scoliosis who have undergone multiple surgical corrections will not have the same spinal anatomy as a healthy patient with no prior spine surgeries. This will need to be taken into consideration when considering both epidurals and paravertebral blocks in patients with bowel obstruction. Furthermore, patients with multiple abdominal surgeries will have distorted abdominal musculature, something to be aware of when performing TAP blocks as a pain management regimen.

40.7.7 Malnutrition and Drug-Drug Interactions

Finally, when evaluating a patient with bowel obstruction, it is important to know their nutrition status and current medication regimen. For example, patients with a poor nutrition status may not be able to tolerate medications such as NSAIDs and opioids as they tend to interfere with the GI tract. For these patients, other alternative medications may be necessary. Similarly, it is important to recognize a patient's current medication regimen. For patients who are on anticoagulation, appropriate timing of the anticoagulant must be obtained in order to safely perform an interventional procedure such as an epidural catheter or TAP block. Alternatively, the presence of anticoagulation may preclude the patient from being eligible for any interventional technique whatsoever. These patients would benefit more from an appropriate multimodal medication regimen.

40.8 Treatment

40.8.1 Aim of Treatment

The ultimate aim of treatment for small bowel obstructions is resolution of the obstruction. The means to achieve relief of obstruction depends on the severity of obstruction, and the criteria listed above. For large bowel obstructions, the aim of treatment can vary depending on the etiology of obstruction. For patients with malignancy related obstruction, the primary aim of treatment is to relieve the obstruction for palliative purposes, i.e. allow the patient to resume normal bowel function for the remainder of their lives. For patients with inflammatory bowel disease related obstruction, the aim of treatment is to eradicate the disease, usually

through surgical resection, to prevent recurrence of obstruction. Patients with a large bowel volvulus require emergent surgical intervention to try and reduce the volvulus, prevent bowel infarction, and thus allow for resolution of obstructive symptoms. Finally, patients with acute colonic pseudo-obstruction syndrome, in which there is no tangible source for obstruction, the aim of treatment is to identify the underlying disorder, and aim to treat that with the hope that it resolves the obstruction.

40.8.2 Preoperative Versus Post: Operative Pain Control

For patients who will either be non-operative management, or who are operative but haven't yet received the operation, pain control relies on trying to relieve obstructive symptoms. Non operative management includes making the patient NPO by mouth, providing parenteral nutrition to ensure metabolic derangements and nutritional deficiencies are corrected, and nasogastric tube decompression to prevent aspiration and provide patient comfort. Most data suggests 65–81% of partial SBO cases without peritonitis can be managed successfully with medical management [16, 17]. Non operative management should be continued for up to 72 h, and surgical options should be considered at that time if there is no resolution in signs or symptoms.

During this time of medical management, it is important to be cognizant of pain control regimens as opioid therapy can further worsen the disease process. A multimodal approach should be considered, including Tylenol, and NSAIDs such as ibuprofen around the clock, and minimal opioid use for breakthrough pain. The most important treatment regimen for pain control is actually resolution of symptoms via bowel rest, and nasogastric tube decompression.

Furthermore, interventional techniques are slowly becoming incorporated into the medical management of small bowel obstructions, including epidural catheters. The theory behind epidural catheters for small bowel obstruction relies more on the correction of the pathophysiology that causes the obstruction rather than controlling the pain. A study by Namoto et al. looked at 70 patients from 1981 to 1990 who received epidural catheters in conjunction with medical management for intestinal obstruction. The epidural anesthesia was used to block both splanchnic and somatic nerves that innervate the bowel, thus allowing for increased peristalsis and gut motility. 48 out of the 70 patients had improvement in clinical symptoms, on average passing flatus 8.3 h after placement of epidural catheter. Furthermore, the 22 patients who had no resolution of symptoms were also expedited to surgical colectomies quicker than with standard medical management, on average 15.4 h after placement of catheter. While still relatively new, epidural catheters could become a mainstay in the medical treatment of both small and large bowel obstructions [18].

Surgical management of small bowel obstruction should be undertaken when signs or symptoms of bowel obstruction have not resolved, or signs of ischemia begin to show. Generally, the primary surgical team managing the patient will determine when and if the patient has failed medical management, and should be prepared for surgery. With surgical treatment, the underlying disease process is

identified and corrected right away, and the management of the post-operative patient switches predominantly to pain control and resumption of bowel function. Along with standard pain management techniques including NSAIDs, acetaminophen, and minimal opioid use, further pain control and expeditious recovery of bowel function could be achieved with interventional techniques. These techniques will be discussed later in the chapter.

40.8.3 Multimodal Therapy

Due to the nature of the disease, bowel obstruction can be further worsened by use of opioids, as they are well known to cause constipation, and an overall delay of intestinal motility. Therefore, it is best to approach patients with both large and small bowel obstructions using a multimodal pain medication regimen. Medications that can be utilized to help alleviate pain in obstructed patients include acetaminophen, selective cox two inhibitors such as celecoxib, gabapentin for post-operative neuropathic pain, serotonin reuptake inhibitors such as tramadol, which have a less potent side effect profile when compared to traditional opioids, and topical local anesthetic patches such as a lidocaine 5% patch. Furthermore, intravenous infusions of both lidocaine and ketamine can be utilized as well as an opioid sparing technique to manage pain control. In a case review by Boysen et al., the use of IV lidocaine was used in a 43-year-old female patient with small bowel obstruction both intra-operatively and in the post anesthesia care unit. With the addition of one dose of Ketorolac 30 mg IV in the PACU, the patient was discharged to the floor safely with a VAS score of 3/10, with resumption of bowel function and toleration of diet on post-operative day 1 [19]. Finally, regional anesthetic techniques such as epidurals, transverse abdominis plane (TAP) blocks, paravertebral blocks can also be used in patients for analgesia.

40.8.4 Regional Techniques

As discussed above, part of the analgesic regimen for bowel obstruction includes regional techniques, utilized both in non-operative and operative settings. The following techniques have been described in prior literature with good relief in patients with bowel obstruction:

1. Epidural catheters—Epidural catheters can be utilized in patients with bowel obstruction for both non operative and operative management. In patients with non-operative bowel obstruction, epidural catheters can lead to faster resolution of obstruction, with one study describing patients passing flatus on average 8.3 h after placement of the epidural. For the operative patient, multiple studies have shown a reduction in pain, and faster return of bowel function in patients with

epidural analgesia in comparison to PCA and standard IV opioid analgesia regimens [20]. Determining the location of placement for epidural catheters depends on the type of bowel obstruction and the medical management of the patient. For patients who will have abdominal surgery to resolve the obstruction, a low thoracic to high lumbar epidural catheter would be best suited, as it would cover the overlaying T8–L1 nerve roots that innervate the cutaneous and visceral abdominal structures of the abdomen. With a typical spread of approximately 2–3 vertebral levels above and below the level of the epidural, a T9–10 or T10–11 epidural catheter would reasonably cover the appropriate region of operative intervention. For patients with non-operative bowel obstruction, it is important to note the origin of the celiac, superior mesenteric, superior hypogastric, and inferior hypogastric plexus. For patients with small bowel obstructions, the celiac, and superior mesenteric plexus play a major role in sympathetic innervation. Blocking this leads to an unopposed parasympathetic tone that acts to increase peristalsis and help improve bowel obstructive symptoms. They arise from the fifth to ninth thoracic nerve roots, and thus an epidural catheter placed in the low to mid thoracic vertebral space, at the level of T7–T9 would result in optimal analgesia and function. For large bowel obstructions, the T10–L2 nerve roots are responsible for the sympathetic fibers that synapse and form the superior and inferior hypogastric plexus, and are the primary target for epidural block. Therefore, an epidural placed in the T12–L1 interspace would yield the best results. The type of local anesthetic used for each epidural is generally up to the discretion of the provider but a continuous infusion of low concentration bupivacaine such as 0.125%, would be preferable. While systemic opioids should be avoided as they can worsen the obstruction, neuraxial opioids are not necessarily contraindicated as they don't cross into the systemic circulation at high enough concentrations to cause or propagate an ileus picture. Catheters should be kept in place until resolution of symptoms is noted for non-operative patients, or until patients are able to be successfully controlled on IV and PO analgesic medications. Generally, if this is longer than 5–7 days, the epidural catheter should be removed to decrease the risk of infections.

2. Single shot transverse abdominis plane blocks or catheters (TAP blocks/catheters)—due to surgical approaches involving transection of the abdominal muscles, patients most often complain of somatic abdominal muscle pain post operatively. This can delay patient's mobility and return of bowel function. To facilitate faster return of mobility and bowel function, post-operative transverse abdominis plane blocks and catheters can be utilized to completely block somatic pain coming from the abdominal muscles. Flor de Lima et al. looked at a single patient case report in which they performed bilateral TAP catheters in a patient undergoing abdominal surgery. Their results yielded a pain score of 0 at both the 24 and 48 h mark [21]. While still relatively new, the utilization of TAP catheters will only increase as the ease and knowledge of ultrasound imaging grows.
3. Celiac, superior hypogastric and inferior hypogastric plexus blocks—Celiac plexus blocks provide a similar approach to pain management and treatment of

small bowel obstructions as epidural catheters. Rather than blocking direct pain fibers and allowing for pain control, celiac plexus block can cause a sympathectomy at the celiac plexus, allowing for an imbalance favoring parasympathetic tone to the small and large bowel. This then allows for an increase in peristalsis, gut motility, and faster return of bowel function. However, caution should be advised regarding solid mechanical obstructions, as performing a celiac plexus block would only further worsen symptoms in these patients. Preferably, the celiac plexus block could work well in patients with post-operative ileus. Similarly, the superior hypogastric and inferior hypogastric plexus blocks work to provide a sympathectomy for patients with large bowel obstruction.

4. Quadratus Lumborum blocks—Utilized for lower abdominal surgery, the quadratus lumborum block is a field block that reliably covers the L1–L3 nerve roots, part of which create the superior and inferior hypogastric plexus that innervate the large bowel. In patients with operative management of large bowel obstruction, a quadratus lumborum block can be utilized for pain control as well as adequate sympathetic blockade to help assist in speedier resumption of bowel function. Recommended doses of local anesthetic include 0.2–0.4 mL/kg of ropivacaine 0.2–0.5% or bupivacaine 0.1–0.25% per side. Caution must be utilized to avoid local anesthetic toxicity. As usual, if a catheter is placed, the recommended time for leaving the catheter in place is until resolution of symptoms, or pain control with IV and PO medications. Catheters should not be left in for longer than 5–7 days due to increased risks for infection [22].

40.8.5 IV Infusions

1. IV ketamine infusion—intractable pain post operatively can be managed by either placing the patient on a patient controlled analgesia (PCA) regimen, or performing one of the interventional techniques described above. However, if interventional techniques are not feasible, caution should be advised against IV opioid PCA regimens as they can further worsen post-operative ileus. If medical providers find difficulty in providing adequate pain control with moderate amounts of opioids, an IV ketamine infusion can be used. Begin with a loading dose of 1–4.5 mg/kg, followed by an infusion rate of 0.1–0.5 mg/min IV. Adverse reactions include hypertension, tachycardia, increased ICP, anaphylaxis and cardiac dysrhythmias. General consensus guidelines recommend against the use of IV ketamine in patients with severe cardiovascular disease [23].
2. IV lidocaine infusion—for patients who fail opioid therapy, are not candidates for interventional techniques, and/or have cardiovascular disease that prevents them from receiving IV ketamine infusions, an intravenous lidocaine infusion can be administered for analgesia. A study by Purper Ortiz et al. in 2016 showed intraoperative and postoperative use of lidocaine showed no difference in patients requiring opioids for further analgesia when compared to an opioid only group.

However, there was a statistically significant decrease in serum inflammatory markers such as interleukin 1 and interleukin 6. Theoretically, a faster drop in inflammatory markers during the active disease state could lead to shorter duration of disease, though this has yet to be proven [24].

40.8.6 Methylnaltrexone

For patients with acute colonic pseudo obstruction, or Ogilivie syndrome, and patients with generalized constipation, methylnaltrexone is an alternate treatment option. A meta-analysis looking at the efficacy of methylnaltrexone lead to researchers finding clear evidence in support of it in relieving constipation in opioid treated patients with advanced illness. Care must be taken to ensure malignancy, if present, does not cause a mechanical obstruction, which could further worsen the obstruction [25]. The mechanism of action of methylnaltrexone is known to be antagonism at the opioid receptor, particularly the mu opioid receptor. By antagonizing the receptor at the level of the intestines, methylnaltrexone is able to prevent inhibition of peristalsis, allowing for the patient's parasympathetic tone to take over, leading to resumption of bowel function.

40.9 Cancer Pain/Palliative Surgery

The most common cause of large bowel obstruction is malignancy. Therefore, depending on the type and severity of the tumor, patients may either be treated with surgical therapy for therapeutic or palliative purposes. In these scenarios, pain management should focus on post-operative pain control with the modalities described above. For patients with non-operative cancer pain, it is recommended for patients to follow up with a pain physician on a regular basis who can manage their pain with both interventional techniques as well as a balanced multimodal pain medication regimen.

40.10 Discharge Plan for Pain Management

For patients with medically managed bowel obstruction, pain is generally well controlled once the active disease process is over. Management at discharge should instead focus on preventing the recurrence of bowel obstruction. For patients with small bowel obstruction, this includes ensuring proper nutrition, such as high fiber intake, and correction of inciting factors, such as elective repair of hernias, is undertaken. Patients can be encouraged to take Tylenol, or NSAIDs sparingly for mild to moderate pain. For patients with large bowel obstruction, the underlying etiology

needs to be the mainstay of focus to prevent further episodes of bowel obstruction. This includes palliative resection of malignant tumors if that is determined to be the source of obstruction. For patients with acute colonic pseudo obstruction syndrome, maintaining proper bowel habits is key to preventing recurrence of bowel obstruction. This includes a regimen of high fiber diet, daily prophylaxis bowel regimen including Peri—Colace and Miralax, and maintaining overall health with proper exercise. Avoidance of opioids in all populations is important in preventing a recurrence of disease.

For patients with surgical management of large and small bowel obstructions, it is important for patients to be discharged on an adequate pain control regimen. While it is not feasible to discharge these patients with epidural or TAP catheters, perhaps performing a single shot block prior to discharge can set them up for better pain control while at home. Furthermore, discharge should be delayed until the patient is appropriately weaned to a minimal amount of opioid use, or else consistent use of opioids at home will bring the disease back. Management of pain at home should include standard therapy, with Tylenol and NSAIDs as the mainstay of therapy. Early use of oral opioids is allowed, but should be weaned off as soon as possible.

40.11 Summary

- Identify bowel obstruction by obtaining a good history, including questions characterizing the pain, and focusing on bowel habits, past surgical history, and similar symptoms in the past.
- Perform a good physical exam, focusing particularly on the abdomen, ensuring to auscultate, percuss, and palpate all abdominal quadrants. Digital rectal exam to evaluate for occult blood, and protruding tumors should be done. Palpation of umbilical and inguinal regions should also be performed to look for hernias.
- Proper blood work including CBC, CMP and lactate levels should be checked to rule out serious pathology including bowel ischemia, sepsis, and septic shock.
- Proper imaging should be acquired, specifically a two-view abdominal x-ray (supine and upright), and CT scan of the abdomen.
- Multidisciplinary approach including the surgical team should be undertaken to determine if the patient should be managed medically or surgically
- For medically managed patients, nasogastric tube decompression should begin immediately, along with proper bowel rest (NPO).
- For surgically managed patients, focus on intraoperative and post-operative pain control
- Pain management in both populations can begin with a multimodal analgesia plan including Tylenol, NSAIDs, and minimal opioid use.
- Epidural catheters can be utilized in both medical and surgically managed patients to provide a sympathectomy leading to faster return of bowel function.

- In surgically managed patients, TAP blocks and catheters, along with celiac plexus blocks can be utilized to relieve somatic pain from abdominal muscles that have been cut during surgery.
- For both populations, IV lidocaine and ketamine infusions can be utilized if pain is uncontrolled with standard therapy.

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Chapter 41
Weight Considerations

Andrew Pfaff and Kristopher Schroeder

41.1 Introduction

The hospitalized morbidly obese patient provides a management challenge to the pain practitioner, particularly those patients with chronic pain or uncontrolled post-surgical pain. To manage these patients effectively, the pain practitioner must understand the altered physiology of the morbidly obese as well as the necessary changes in both pharmacologic and non-pharmacologic interventions to keep these patients safe. This chapter presents the epidemiology and pathophysiology of obesity and the impact obesity has on the relative merits of available multimodal analgesic options.

The concept of the body mass index (BMI), originally termed Quetelet index, began with Belgian mathematician and statistician Adolphe Quetelet in the nineteenth century, who postulated that a person's weight was roughly proportional to the square of a person's height [1, 2]. (It should be noted that, by the very existence of obesity, that this proportionality is not a universal constant.) Obesity is typically defined as a BMI greater than or equal to 30 kg/m^2 with several classes depending on the severity: class I from 30 to less than 35, class II 35 to less than 40, and class III 40 or greater [3]. The term "morbid obesity" is generally reserved for patients with a BMI between 40–50 kg/m^2 or a BMI greater than 35 kg/m^2 with associated obesity-related health concerns. The worsening obesity epidemic has required an increase in our descriptive vernacular such that patients with a BMI between 50–60 kg/m^2 are considered super morbidly obese and those with a BMI greater than 60 kg/m^2 are considered super-super-morbidly obese. Increased BMI is associated with an elevated risk for development of diabetes, heart disease, stroke,

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hypertension, and hyperlipidemia, among other conditions [4, 5]. BMI has limitations, given that it does not measure body fat directly. BMI's association with body fat varies by age, sex, race, and Hispanic origin [6, 7]. Furthermore, the BMI at which the increased risk for obesity-related conditions begins may vary among race groups [8, 9]. Nevertheless, BMI correlates moderately well with other measurements of body fat including skinfold thickness measurements, bioelectrical impedance, underwater weighing, and dual energy X-ray absorptiometry [10–14]. Thus, BMI still serves as a useful screening tool for obesity and obesity-related conditions. Further discussion of the limitations of BMI is beyond the scope of this chapter.

Recent CDC data demonstrates that the incidence of obesity continues to rise. Data released in 2017 reveals an obesity prevalence of 39.8% in adults and 18.5% in youth in the years 2015–2016, as defined by a BMI $\geq$ 30 [15]. This reflects a steady increase from 30.5% in adults and 13.9% in youth since the years 1999–2000 [4]. Middle-aged patients (40–59 years old; 42.8%) are affected more than younger patients (20–39; 35.7%); similarly, Hispanic and non-Hispanic black patients are affected more than non-Hispanic Asian and white patients [16]. These estimates are significantly higher than the Healthy People 2020 goals for obesity prevalence of 30.5% among adults and 14.5% among adults. Taken together, these figures demonstrate the increasing burden that obesity is placing on the healthcare system while concomitantly emphasizing the need for the pain practitioner to understand how to manage the obese patient effectively.

41.2 Pathophysiology

Obesity impacts multiple organ systems, including the respiratory, cardiovascular, gastrointestinal, endocrine, and metabolic systems. These effects change the pharmacokinetics of the obese patient, complicating how to best utilize pharmacologic analgesics in these patients. Understanding the interplay of these organ systems and pharmacologic changes informs how the pain practitioner manages the obese patient with acute or chronic pain.

Obese patients have increased oxygen consumption (VO_2) and carbon dioxide production (VCO_2), despite maintaining a normal basal metabolic rate [17]. The increased VCO_2 necessitates a higher minute ventilation (VE) to maintain normocarbia; however, as the ability to increase VE has limits, at extremes of obesity, patients can develop obesity-hypoventilation syndrome, characterized by the loss of hypercarbic respiratory drive brought on by chronic hypercarbia [17]. Although lung compliance remains normal, this is overridden by decreased chest wall compliance, which can result in overall a restrictive lung disease. Expiratory reserve volume (ERV) and functional residual capacity (FRC) are decreased (an effect worsened with supine positioning) [17]. Tidal volume can approach closing capacity (CC) with concomitant ventilation-perfusion (V/Q) mismatch and hypoxemia [17]. Combined, these factors predispose the obese patient to respiratory

depression following the administration of medications with sedative properties. This increased predisposition to respiratory depression can trigger hypoxic pulmonary vasoconstriction, further worsening the baseline pulmonary hypertension that is frequently present in obese patients.

Cardiac output, blood volume, and plasma volume increase proportionally with VO_2. Increased stroke volume is the main mechanism of increased cardiac output [17]. The increased blood flow is primarily directed toward the splanchnic circulation [17]. Blood flow to the site of action of many analgesics (e.g., brain) remains relatively constant in obese patients. Therefore, most analgesic dosing should be based on ideal rather than total body weight. Arterial hypertension is more common in the obese population [4, 17]. Increased circulating volume and arterial hypertension effectively create increased preload and afterload for the heart, but the clinical significance of this difference on the provision of analgesia is unclear [17].

Obese patients are considered to be at increased risk for aspiration of gastric content secondary to their increased prevalence of hiatal hernia and increased intra-abdominal pressures [17]. Increased durationof obesity increases liver fat content, which is often not detected on typical hepatic laboratory studies [17]. The presence of hepatic steatosis (either suspected or present on abdominal imaging) should alert the pain practitioner to possibledecreased metabolism and clearance of medications that undergo hepatic metabolism or elimination. Dyslipidemia, hyperglycemia, insulin resistance, and frank diabetes mellitus are more common in the obese population [4, 17]. Hyperlipoproteinemia can impact plasma protein concentration, which has implications for drug-protein binding and drug metabolism [17].

41.3 Pharmacokinetics and Dosing Scalars

The physiologic changes described above alter the pharmacokinetic properties of most drugs. In addition to increased fat, obese patients also possess increased lean body weight (LBW) compared to non-obese patients matched for gender, age, and height. As much as 20–40% of the excess TBW can be attributed to increases in LBW [18, 19]. The altered LBW-to-TBW ratio, along with the changes in total and regional blood flow and the increased cardiac output, can greatly alter the volume of distribution, clearance, and elimination half-life of medications [18, 20]. The hepatic or renal dysfunction often found in the morbidly obese can compound these alterations in biotransformation and clearance [17]. As a corollary, the pharmacodynamics (and thus the adverse effects) of many drugs can be more pronounced in morbid obesity. For example, when sedating analgesics are administered to an obese patient with poor baseline respiratory mechanics, precipitous respiratory depression can occur. One can think of this as a narrowed therapeutic window for many drugs in the morbidly obese population [21].

In general, lipophilic drugs have an increased volume of distribution and longer elimination half-life due to the large fat compartment in the obese patient. This longer elimination half-life holds true even if clearance *per se* is not reduced, as the drug

must be redistributed from the fat compartment before it can be cleared [17]. In contrast, hydrophilic drugs generally have similar volumes of distribution, elimination half-lives, and clearance times in non-obese versus obese patients [17].

When determining the dose of a drug, weight is considered along with age, gender, and comorbidities. Due to their altered body composition and physiology, TBW is typically inappropriate to guide drug dosing in the morbidly obese. Several dosing scalars have proposed to replace TBW in the morbidly obese population. These include ideal body weight (IBW), LBW, body surface area (BSA), and allometric scaling. Below is a discussion of each of dosing scalars commonly used in clinical medicine.

41.3.1 Total Body Weight

In the non-obese patient, TBW approximates IBW and LBW. However, in the morbidly obese, the increased body fat results in a lower LBW:TBW ratio [22]. Recalling that the increased cardiac output in the morbidly obese is primarily to the splanchnic circulation, the cardiac output to the site of action of many analgesics (i.e., the vessel-rich and lean tissue groups) remains relatively constant [21]. Basing dosing off of TBW can thus lead to analgesic overdose, limiting TBW's usefulness in the morbidly obese.

41.3.2 Ideal Body Weight

First described by Devine in 1974, IBW is defined as the weight associated with the greatest life expectancy for a patient of a given height and gender [23]. Various equations, all of which produce similar values, have been proposed to calculate IBW. One limitation to IBW is that it does not account for the degree of obesity that a patient has, as it is primarily based on height. Furthermore, recalling that 20–40% of an obese patient's increased TBW is attributable to increased lean body mass, it follows then that IBW is typically less than LBW. As the LBW is analogous to the vessel-rich and lean tissue groups where many analgesics work, using IBW as a dosing scalar may result in underdosing of drugs [21].

41.3.3 Lean Body Weight

LBW is defined as the difference between TBW and fat mass. As previously mentioned, in morbid obesity, absolute lean body mass increases while the ratio of LBW:TBW decreases. Due to its significant correlation with cardiac output,

early drug distribution kinetics, and drug clearance, LBW appears to the be ideal dosing scalar for the morbidly obese patient [24–26]. Unfortunately, LBW can be difficult to accurately determine in everyday clinical scenarios. James' equation, commonly used to calculate LBW, has been shown to underestimate LBW in extreme morbid obesity [27, 28]. Some newer equations for LBW have been shown to better reflect the pharmacokinetics of analgesics in the morbidly obese, so the concern for an inaccurate calculation LBW is diminishing [21].

41.3.4 Body Surface Area

BSA is the scalar typically used for the dosing of chemotherapy. Mosteller's equation, the most commonly used, calculates a surface area using height and TBW. As it does not differentiate between lean and fat body mass, BSA has the same limitations as using TBW for drug dosing in the morbidly obese [21].

41.3.5 Allometric Scaling

Allometry is the study of the relationship of body size to shape and physiology. Allometric scaling has been used to extrapolate veterinary medicine principles to human clinical medicine as well as adult data to pediatric populations [21]. Currently, few researchers have used allometric principles to estimate drug pharmacokinetics in the morbidly obese using data from normal weight patients. While it has promise in guiding drug dosing in the morbidly obese, allometry requires much more study before it can be used in clinical practice.

41.4 Management of Pain in the Inpatient Setting

41.4.1 Pharmacologic Agents

The ideal analgesic regimen for the obese patient should be multimodal and non-sedating, which typically means opioid-sparing. Acetaminophen, NSAIDs, GABAergics, and regional analgesic techniques are all viable options to minimize opioid usage and limit the respiratory depression associated with heavy opioid use. Most often, the dosing of these medications should be based on IBW or LBW. There are number of tables and calculators available to assist with determining these figures. Alternatively, this information is frequently provided in a patient's electronic medical record and should be readily available for review prior to analgesic dosing.

41.4.1.1 Opioids

Opioids do have a role in the pain management of the morbidly obese, although that role is limited by their proclivity to induce respiratory depression. Considering the downstream effects of the three opioid receptors, mu, kappa, and delta, mu receptor agonists provide the most profound analgesia but are also associated with the development of respiratory depression [29]. Thus, while opioids that function as profound mu receptor agonists (i.e. morphine and fentanyl) provide significant analgesia, they possess a narrower therapeutic window in the morbidly obese than the kappa and delta agonists. This does not imply that the analgesia provided by kappa agonists is insignificant; however, the dysphoria from kappa agonists has limited the usefulness of opioids such as butorphanol and nalbuphine in clinical practice [30]. Kappa agonists that cause less dysphoria by acting peripherally rather than centrally are in development, promising a potential alternative to those opioids currently commercially available [30]. Agonist effects at the delta receptor do potentiate the analgesic effects of mu and kappa agonists, although no opioid currently available acts selectively at the delta receptor.

A full discussion of all the various opioids available is beyond the scope of this chapter. Few studies have examined opioids as a solitary modality for the provision of postoperative analgesia in the morbidly obese. Expert opinion, however, clearly advises limiting the use of patient-controlled analgesia (PCA) to patients with moderate to severe pain, avoiding basal opioid infusions, monitoring respiratory status via pulse oximetry as long as a PCA is in use, and converting to oral opioids as soon as possible [31]. Tramadol, an opiate with multimodal serotonergic and noradrenergic effects, is part of step II the World Health Organization's (WHO) analgesic ladder and may be appropriate for those morbidly obese patients with mild to moderate pain [32]. Each opioid possesses differing potency and thus differing dosing recommendations. As each opioid's potency can be graded in terms of morphine equivalents, calculators exist that can convert the current dosage of one opioid to another, even accounting for cross tolerance if a patient is a chronic opiate user.

41.4.1.2 Acetaminophen

Acetaminophen, or paracetamol, is an invaluable medication in the obese population as it is easily available, has many routes of administration, has a safe side effect profile and thus few absolute contraindications. Despite its first synthesis in 1877, the mechanism of acetaminophen is not well known. It appears to inhibit cyclooxygenase (COX) in the central but not the peripheral nervous system (hence it is not anti-inflammatory) and may even modulate the endogenous cannabinoid system [33]. Acetaminophen can be administered by oral, intravenous, or rectal routes. While associations between acetaminophen and asthma, Stevens-Johnson syndrome, and certain renal cancers have been observed, acetaminophen is typically safe unless taken in an overdose, where it is hepatotoxic and may cause fulminant liver failure. Based on clinical data, acetaminophen dosing should be based on ideal

body weight. Typical dosing is 12.5–15 mg/kg every 6 h up to 1000 mg per dose, with a total daily dose of up to 75 mg/kg/day or 4 g/day. Dosing adjustment is not required in renal disease. Dose reduction is not well studied in patients with hepatic disease, but given the drug's ability to invoke hepatotoxicity, recommendations typically suggest limiting the total daily dose to 2–3 g/day.

41.4.1.3 Non-steroidal Anti-inflammatory Drugs

There are various non-steroidal anti-inflammatory drugs (NSAIDs) available to the pain practitioner. This class of medications provide analgesia by inhibiting cyclooxygenase (COX) 1 and/or 2, leading to decreased prostaglandin and thromboxane synthesis. Decreased prostaglandin and thromboxane levels, in turn, limit inflammation and impede blood clotting, respectively [34]. The NSAIDs ibuprofen, aspirin, naproxen are inexpensive, available over the counter and commonly self-administered. However, there are many more NSAIDs available via prescription, including the COX-2 selective "coxibs" (e.g., celecoxib), the "oxicams" (e.g., meloxicam), and ketorolac. Each NSAID possesses a unique side effect profile. Potential complications related to NSAID administration include GI upset/ulceration due to decreased prostaglandin; increased bleeding risk due to decreased thromboxane; increased heart attack and stroke risk except with aspirin, which is protective; and the potential for chronic kidney disease with chronic use. In the inpatient with intravenous access who cannot take over-the-counter oral medications, IV ketorolac is a commonly prescribed NSAID. Based on clinical data, IV ketorolac dosing should be based on ideal body weight. Typical dosing is 0.5 mg/kg every 6 h up to 15–30 mg per dose, with a total daily dose of up to 60–120 mg/kg. Caution should be used in advanced renal disease, elderly patients, or patients weighing less than 50 kg, all of whom may be at risk for renal impairment or GI ulcerations or bleed. No dosage adjustment is needed for hepatic impairment.

41.4.1.4 Ketamine

Ketamine, an NMDA receptor antagonist, possesses clinical utility as an anesthetic, a sedative, and (in low doses) an analgesic. In the obese population, ketamine's appeal is derived primarily from its ability to preserve airway reflexes and respiratory drive. One RCT demonstrated that the addition of low-dose ketamine to an IV morphine PCA leads to reduced opioid consumption while improving oxygen saturation and decreasing the frequency of desaturation episodes in the postoperative period [35]. Other studies have demonstrated decreased intra- and postoperative opioid use with either bolus or infusion ketamine regimens [21]. Based on clinical data, IV ketamine should be dosed relative to a patient's ideal body weight. Doses of 0.2–0.8 mg/kg up to a maximum dose of 50 mg have been used to provide postoperative analgesia as part of an opioid-sparing protocol; however, these higher doses do have the potential for sedation. Lower doses of 0.1–0.5 mg/kg have the

potential to be a safe adjunct to an analgesic regimen while minimizing sedation. Ketamine does not require dose reduction in hepatic or renal disease. Other side-effects related to the administration of ketamine are relatively infrequent but could include visual disturbances or hallucinations.

41.4.1.5 GABAergics

Pregabalin and gabapentin are well known for their use in chronic, neuropathic pain, but they may also have a role in the treatment of acute postoperative pain. A single preoperative dose of pregabalin has been shown to decrease morphine consumption, postoperative pain scores and postoperative nausea and vomiting [36]. Based on clinical data, pregabalin dosing should be based on ideal body weight. There is no consensus for the dose, frequency, or duration of use of pregabalin. For chronic neuropathic pain, dosing typically begins at 25–150 mg/day and is incrementally increased to a total daily dose of 300–600 mg/day. In lower weight patients, the recommended dose for this indication is between 2.5–3.5 mg/kg/day. This is contrasted with off-label use for post-operative pain, where a single dose of 75–300 mg is administered 1–2 h prior to surgery. There does not seem to be a benefit to additional postoperative doses [37]. Dosing is unaffected by hepatic disease but dependent on creatinine clearance in renal disease. As both pregabalin and gabapentin are known to cause sedation and alter sleep architecture, caution must be used if the patient has OSA associated with their obesity [21]. Overall, a single preoperative dose of gabapentin or pregabalin may help reduce postoperative opioid consumption without contributing too greatly to sedation or respiratory depression. The elderly, in particular, seem to represent a high-risk group for the development of sedation with gabapentin therapy. Nausea represents an additional common side effect of gabapentin that may limit more widespread application.

41.4.1.6 Alpha-2 Agonists

The alpha-2 agonists, dexmedetomidine and clonidine, are increasingly used intraoperatively as anesthetic and analgesic adjuncts, particularly in the morbidly obese population. Action at both spinal and supraspinal alpha-2 receptors appears to contribute to the drugs' analgesic effects. Dexmedetomidine, in particular, is commonly used as part of enhanced recovery after surgery (ERAS) protocols in bariatric surgery, where it has been found to decrease opioid consumption, decrease postoperative nausea and vomiting risk, and expedite PACU discharges [38]. Both dexmedetomidine and clonidine can result in sedation, bradycardia, and hypotension, although the effects seem to be more pronounced with clonidine. Given that pain scores, opioid consumption, postoperative nausea and vomiting incidence, and patient satisfaction between patients who receive clonidine versus dexmedetomidine are similar, dexmedetomidine may be the preferred alpha-2 agonist in the obese patient population secondary to a diminished incidence/severity of sedation

and improved hemodynamic stability [39]. Based on clinical data, dosing of dexmedetomidine is currently based on actual body weight, although pharmacodynamic and pharmacokinetic studies in the morbidly obese are lacking. A bolus of 0.5–1 μg/kg can be given over 10 min, followed by an infusion of 0.2–0.9 μg/kg/h as tolerated hemodynamically. No dose adjustment is required in renal or hepatic disease.

41.4.1.7 Intravenous Lidocaine

Intravenous lidocaine has been well studied as an analgesic in abdominal surgery, and its use has begun to expand to other acute and chronic pain indications. An amide local anesthetic, lidocaine functions via blockade of sodium channels in nerve tissues [40]. Intraoperative IV lidocaine has been shown to decrease opioid consumption for up to 24 h following certain surgical procedures [41]. Lidocaine has an extremely safe side-effect profile apart from local anesthetic systemic toxicity (LAST), which first presents with central nervous system depression and culminates in cardiovascular collapse. Multiple dosing regimens have been used to treat acute pain, including fixed boluses of 50–100 mg, adjusted body weight boluses of 1–2 mg/kg, and an adjusted body weight infusion of 1 mg/kg/h [41]. Given the variety of dosing regimens, the proper dosing in obesity is not known. Taking into account its narrow therapeutic index and its potential for life-threatening adverse effects, a fixed bolus of 100 mg every hour may be a prudent maximum dose. Further dose reductions should be considered in the presence of hepatic disease secondary to a diminished ability to metabolize lidocaine and in cardiac disease where LAST could occur at lower doses.

As an aside, there are various topical formulations of local anesthetics. These include lidocaine patches; lidocaine, benzocaine, prilocaine, or tetracaine ointments, gels, or creams; or even a mixture of local anesthetics such as EMLA cream (Eutectic Mixture of Local Anesthetics of lidocaine and prilocaine). These topical medications do not treat visceral, only cutaneous, sources of pain. Overdose with these medications is possible. The maximum recommended dose for a 5% lidocaine patch (containing 700 mg of lidocaine) is 3 patches for up to 12 h in a 24-h period. Due to the risk of LAST, these topical local anesthetics should be not used in combination with intravenous lidocaine or other regional anesthetic or analgesic techniques.

41.4.2 Regional Anesthesia and Analgesia

As a non-sedating method of producing profound analgesia, regional anesthetic blockade would appear to be the ideal method of pain control for the obese patient. The placement of perineural catheters can extend the analgesic duration of blockade for beyond 24 h. However, performing regional blockade in the obese patient provides it owns challenges. Additional body fat can distort anatomy, and indistinct

landmarks can complicate regional techniques performed by palpation. However, proper planning including the use of peripheral nerve stimulation and ultrasound can minimize these difficulties.

41.4.2.1 Truncal Blocks

Transversus abdominis plane (TAP) blocks and quadratus lumborum plane (QLB) blocks can be performed pre- or postoperatively for a variety of abdominal procedures. Depending on the exact deposition of local anesthetic, TAP blocks can provide sensory blockade from T6-T12 dermatomes, and QLB blocks can extend this blockade from T4-L1 [42, 43]. In laparoscopic surgery in the obese, however, these blocks do not appear to be superior to infiltration of local anesthetic at trocar sites. Intraperitoneal infusions of local anesthetic postoperatively have also been described but are not well studied [44].

A variety of blocks exist for chest wall analgesia, including paravertebral (PVB) blocks, erector spinae plane (ESP) blocks, pectoralis nerve blocks, serratus plane blocks, and intercostal nerve blocks. The efficacy and failure rate of these blocks in the morbidly obese has not been described. As the failure rate of these blocks are highly dependent on operator experience, it is recommended that these blocks are done by a proceduralist who routinely performs the desired block. Pneumothorax, secondary to an errant needle utilized for paravertebral blockade, could be catastrophic in a morbidly obese patient.

41.4.2.2 Neuraxial Analgesia

Data on epidural analgesia in the obese population comes primarily from the obstetric literature. Epidural analgesia, while technically difficult, provides effective analgesia with less postoperative nausea and vomiting, earlier ambulation, and less respiratory depression, even if epidural opioid is used [45]. Futhermore, the use of epidural analgesia confers additional cardiac and respiratory benefits such as decreased VO_2, left ventricular work, and shunt fraction [17].

41.4.2.3 Extremity Blocks

While a detailed discussion of each of the numerous blocks that can be performed for the upper and lower extremities is beyond the scope of this chapter, the interscalene and the supraclavicular block deserve mention as blocks associated with an elevated risk of respiratory compromise. Although the use of ultrasound has greatly diminished the risk of pneumothorax during a supraclavicular block, both interscalene and supraclavicular nerve blocks can result in phrenic nerve blockade and hemiparesis of the diaphragm.

Diaphragmatic paralysis can have a profound impact on obese patients following interscalene blockade. In an observational trial, obese patients with diaphragmatic paralysis were found to be at increased risk for the development of dyspnea, hypoxia and failure to achieve discharge status [46]. In an effort to maintain analgesia and minimize the impact of interscalene blockade on diaphragmatic function, a variety of different strategies have been evaluated. Previous research has demonstrated that the use of decreased volumes of local anesthetic (20 vs. 5 mL 0.5% ropivacaine) significantly decreases the impact of interscalene blockade on FEV1, FVC, PEF and postoperative desaturation [47]. In addition, the use of ultrasound-guidance has also been shown to decrease the impact of interscalene blockade on diaphragmatic function [48]. Extrafascial, as opposed to between the C5–6 nerve roots, has been recently demonstrated to decrease diaphragmatic paresis from 90 to 21% [49].

While attempting to minimize the injected volume of local anesthetic and limiting the injection of local anesthetic to positions lateral to the brachial plexus, there is no absolutely reliable way to totally eliminate the risk of phrenic nerve blockade during the performance of an interscalene block. Therefore, in the morbidly obese and those at significant risk for the development of respiratory depression in the setting of diaphragmatic paralysis, alternatives to interscalene blockade should be considered. One possible approach to provide postoperative analgesia following shoulder procedures in the obese would involve an axillary and suprascapular nerve block.

41.4.2.4 Regional Anesthetic Dosing

Based on clinical data, local anesthetics should be dosed based on ideal body weight. Highly vascular planes should be dosed more cautiously, as their rapid uptake of local anesthetic could lead to a greater risk of LAST. Local anesthetics have the most rapid uptake from the trachea, followed by the intercostal space, the caudal space, the paravertebral space, the epidural space, the brachial plexus, the intrathecal space, the sacral plexus and lower extremities, and subcutaneous tissues, in descending order [50]. Thus, the dose of local anesthetic should be based not just on the obese patient's ideal body weight but also on the location of the block.

41.4.2.5 Technical Considerations

As mentioned above, regional anesthesia in the obese patient can be significantly more challenging in obese patients relative to patients of normal weight. Strategies to increase the success of regional anesthesia techniques in this patient population are discussed below.

Proper planning is required to perform regional anesthesia efficiently and effectively in the obese patient. These patients may require additional time to complete their procedures. If a procedure is planned for the sitting or lateral position,

ensure that adequate support staff is available to facilitate positioning without exposing this staff to avoidable musculoskeletal strain. If possible, consider the use of a positioning device to facilitate safe and stable patient positioning. Patient positioning can also make a profound impact on the ability to successfully provide regional anesthesia services to obese patients. For example, arm abduction and external rotation during the performance of infraclavicular blockade can significantly decrease nerve target depth. Performing transversus abdominis plane (TAP) blocks in the lateral position may offer similar benefits.

The pre-procedure discussion in obese patients should also include a description of the potential impact of nerve blockade given the patients increased body habitus (i.e. potential increased risk for dyspnea following interscalene block or falls with lower extremity blocks). These patients should also understand that for certain regional anesthesia procedures (i.e. paravertebral blockade) the procedure may either be terminated or transitioned to a more easily visualized procedure (i.e. erector spinae block). These patients should also be aware that there may be an increased risk of needing unexpected inpatient admission following ambulatory surgery secondary to respiratory issues following regional anesthesia procedures that may impact the phrenic nerve. Finally, nerve visualization can be challenging in obese patients and therefore first identifying large vascular landmarks may assist in nerve localization.

Providing adequate sedation to obese patients undergoing regional anesthesia procedures can be significantly challenging as these patients may be more susceptible to the sedative effects of opioids and benzodiazepines. In addition, procedure duration may be significantly increased in these patients. Therefore, providing procedural sedation via a continuous infusion technique may be advantageous. In addition, the use of agents less likely to produce respiratory depression (i.e. dexmedetomidine) may offer significant advantages.

Obese patients have deeper nerve targets, necessitating the use of longer needles. Increased needle depth is often accompanied by a steeper angle of needle insertion, limiting the ability to visualize the needle. In these cases, it may be advantageous to make efforts to position the target such that the angle of needle insertion can be decreased to improve needle visualization. This can be accomplished via changing the target position on the ultrasound screen or via positioning changes that decrease target depth. The use of echogenic needles, ultrasound machine software enhancements designed to improve needle visibility, or the use of needle guides may also be helpful in bariatric patients.

Contemporary ultrasound equipment offers significant advantages over landmark techniques or peripheral nerve stimulation when performing regional anesthesia in obese patients. Important concepts to consider are that lower frequency probes or settings may be more efficacious for providing images at significant depth. Therefore, ensuring that adequate ultrasound equipment is available is crucial to providing effective regional anesthesia in obese patients.

As nerve and needle visualization becomes more challenging, the use of a dual-endpoint nerve localization technique may improve the chance of successful blockade. Utilization of nerve stimulation as an adjunct to ultrasound guidance may simultaneously assist in nerve structure identification and avoidance of intraneural

injections. For epidural placement, consider the use of nerve stimulation, fluoroscopy, epidural pressure waveform analysis, or commercially available loss of resistance syringe modification devices to confirm the correct placement of an epidural catheter. The use of ultrasound may also help to serve as a dual-endpoint technique to assist in the identification of the anatomic midline or identify the depth to the epidural space.

In the obese patient, it is critical to consider the potential risks, outcomes and difficulty associated with regional anesthesia procedures. For example, as mentioned above, in obese patients at risk for respiratory compromise with phrenic nerve blockade undergoing shoulder procedures, substitution of an interscalene blockade for axillary and suprascapular nerve blocks may provide adequate analgesia without the risk of respiratory depression. Similarly, in patients expected to produce significant difficulties with thoracic epidural catheter placement, substitution of fascial plane blocks may provide adequate analgesia and a more acceptable risk/benefit profile.

41.5 Summary

- Obesity, defined as a BMI $\geq$ 30 kg/m^2, is becoming more common in clinical medicine. Obese patients have altered cardiac and respiratory physiology, as well as associated comorbid conditions, that place them at risk for respiratory depression with sedating analgesics.
- Ideal body weight and lean body weight are appropriate dosing scalars in obese patients, as these account for the relatively constant blood flow to the vessel rich organs and the small but significant increase in lean body mass observed in obesity.
- The ideal analgesic regimen for the obese patient should be multimodal and non-sedating, which typically means opioid-sparing. Acetaminophen, NSAIDs, GABAergics, and regional analgesic techniques are all viable options to minimize opioid usage and limit the respiratory depression associated with heavy opioid use
- Given the technical difficulties of performing regional anesthesia in the morbidly obese, proper planning is required for a successful block, including patient education, adequate support staff, careful patient positioning, use of ultrasound or dual-endpoint techniques, and judicious block selection.

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Chapter 42
Urine Drug Screening in the Hospital Setting

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42.1 Introduction

One of the many indications for UDS testing in the inpatient setting is to screen for the use of exogenous drugs, namely drugs of abuse (DOA). The mechanism of UDS testing involves use of enzyme-linked immunoassays (EIA), which use antibodies for the detection of drug metabolites in the urine [1]. UDS testing is useful as a quick screen to evaluate medication adherence and illicit drug use [1]. Providers also use UDS in patients with suspected drug toxicity and overdose. However, a UDS is simply intended to be a screening tool; a confirmatory test is required for a definitive answer, of which the gold standard is gas chromatography-mass spectrometry (GC-MS) [1]. GC-MS can quantify the amount of drug present, while UDS only shows whether the drug is present or not within the standarts of the UDS-specific drug detection limits. In most situations, clinicians utilize the UDS to guide clinical decision making due to time and cost constraints. Notably, there are limitations to the UDS, including the high rate of false results, which will be discussed in this review.

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42.2 Indications

In the acute setting, UDS testing can be useful to both screen for suspected drug use and drug diversion. While a healthy dose of suspicion should always be maintained for possible drug overdose, a UDS can serve to further these suspicions to direct appropriate, goal directed management. However, providers should also be cognizant of the high false positive and negative rates and therefore rely on other assessment modalities. Careful and appropriate drug screening and confirmation is necessary to avoid unintended consequences of inappropriate interpretation which can range from incarceration, unemployment, mistrust of healthcare providers, and suboptimal treatment.

Persons with acute pain syndromes who present for emergent or inpatient level of care warrant UDS testing to identify individuals that may be abusing opiate medications. Persons who screen positive for opiates should be surveyed in the prescription drug monitoring program to differentitate those with appropriate, chronic opiate use from those with opiate use secondary to illicit substances or diverted medications. Nonetheless, providers should recognize that persons with substance use disorders may also have organic acute pain syndromes, for which the use of non-opiate medications and non-pharmacologic modalities should be optimized. Furthermore, if drug diversion is suspected, repeat UDS testing and presence of medication specific metabolites can help to confirm compliance of opiate medications. Should repeat UDS testing in patients prescribed opiate medications fail to reveal the presence of the specific opiate medication or its metabolites, the possibility of drug diversion should be strongly considered. Consequently, early and possible repeat UDS testing can help providers not only judiciously prescribe opiate medications for the correct indications and appropriate patient, but also prevent the inappropriate distribution of opiate medications in settings of suspected abuse and/or diversion.

42.3 Drugs and Metabolites

There are a variety of drug panels available, with varying applications depending on the clinical setting and objectives. Most panels will test for the five drugs required by federal guidelines: amphetamines, cocaine, marijuana, opioids, and phencyclidine (PCP).

Amphetamines are stimulants used medically for a variety of conditions such as ADHD and narcolepsy. Recreationally, they are used to increase cognitive control, induce euphoria, and enhance athletic performance. EIAs can detect amphetamines, their isomers, and related metabolites such as methamphetamine, methylenedioxyethylamphetamine (MDEA), methylenedioxymethylamphetamine (MDMA), and many more [1–3]. Of note, pseudoephedrine, bupropion, or even ranitidine are some of the common culprits for producing false positive amphetamine UDS results [1–3]. Amphetamines remain detectable in the urine for 48 hours, on average [1–3].

Cocaine is a potent central nervous system stimulant that induces an intense state of euphoria and increases agitation and alertness. It can be used medically as a topi-

cal anesthetic, commonly used for ophthalmic and otolaryngology procedures, where its vasoconstrictive properties may be advantageous. However, the use of topical cocaine for anesthetic purposes is rare and declining. In a UDS, cocaine is detected via its metabolite, benzoylecgonine [1]. Unlike amphetamines, cocaine possesses less cross-reactivity [1]. Cocaine remains detectable in the urine for 2–4 days [1–3].

Marijuana, or cannabis, is a psychoactive drug that induces euphoria and heightened sensations and perceptions. It can be used medically for patients with cancer or AIDS who have chemotherapy-induced vomiting, chronic pain syndromes, and/or anorexia. A UDS for marijuana screens for 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid, its primary metabolite [1]. Efavirenz, an antiviral agent used in the treatment of HIV, has been shown to cross-react with marijuana and result in a false-positive result [1]. Marijuana detectability in the urine varies according to chronicity of patient use and type of marijuana (synthetic vs. organic). The urine dectability of marijuana is directly correlated with chronicity of use. A single, isolated use may remain in the urine for up to 5–7 days, whereas chronic daily use may remain in the urine for up to 45–60 days [1–3].

Opioids are substances that activate opioid receptors in the body, largely found in the central nervous system, to produce analgesic benefit. Opioids can be highly addictive and are often used illicitly for their europhic benefit. Morphine is commonly tested for on routine EIAs as a surrogate for opioids. The difficulty in interpreting UDS results for opioids is secondary to the myriad of opioid derivatives. Morphine possesses little to no cross-reactivity with other opioid derivatives, so opioid compounds such as fentanyl and methadone must be screened for using their specific immunoassay tests [1]. A recent raise in the cutoff levels for morphine detection, in hopes of avoiding incidental positive findings from poppy seed ingestion and prescription opiate use, may have likely also increased the prevalence of false negatives [1]. Opioids remain in the urine for about 48 hours [1–3].

PCP is a drug used for its multisensory stimulatory properties. It has been proven to cross-react with many different drugs and agents, including but not limited to: tramadol (analgesic), ketamine (analgesic), venlafaxine (antidepressant, neuropathic pain), lamotrigine (anticonvulsant), methylendioxyprovalerone (MDPV, "bath salts") [1]. PCP levels remain detectable in the urine for approximately 8 days [1–3].

Tricyclic antidepressants (TCA) are commonly used medications for a plethora of conditions including depression, attention deficit hyperactivity disorder, chronic pain, and chronic headache conditions including migraines. The UDS for TCAs screens positive for a discrete cutoff level of nortriptyline, which conveys active use of amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, or trimipramine medications. Screening for TCA use can helpful in ensuring patient compliance.

42.4 False Positives and False Negatives

A negative result on a UDS can be interpreted in a few different ways. Firstly, it could indicate that the detection window has passed and the drug has been cleared [4]. Secondly, the substance may not be tested for by the chosen urine drug panel [4].

Thirdly, the detection limit may be too low such that the substance may be present but undetected due to the higher cuttoff limits [4]. Fourthly, there could be a falsification of the obtained specimen [4].

The federal cutoff levels are established by the Department of Health and Human Services to differentiate positive and negative results. A low cutoff level leads to greater rate of false positives, while a higher cutoff level leads to a greater rate of false negatives. Depending on the laboratory and setting (e.g. workplace vs. hospital), the exact screening cutoffs may be different. Thus, the interpretation of false negatives and false positives must be considered in the context of the chosen laboratory detection limits.

Another issue with interpretation of UDS results involves falsification, or adulteration, of a urine sample. One can tamper with a urine sample by dilution, addition of substances, or substitution. Within vivo adulteration, there are commercially available products to increase metabolism of DOA, such as Detox XXL Drink or Ready Clean Gel capsules [5]. With dilution, people can simply consume a large amount of water to dilute the urine or, if they are not being monitored during urine collection, add water to the voided urine sample [5]. There are countless ways to tamper with urine through the addition of various non-oxidizing and oxidizing substances. Substitution involves passing another urine sample as your own, through obtaining another person's urine or, in the cases of direct observation, even providing synthetic urine (SU), which can be delivered using via a prosthetic devices with bladder reservoirs [5]. The mechanisms by which chemicals adulterate urine samples are many and include oxidation to destroy compounds, pH alterations, protein denaturation, and antigen-antibody interference [5]. All of these effects may render the screening and confirmatory tests invalid or inconclusive, further complicating the interpretation of UDS results (Table 42.1).

Table 42.1 Standard illicit drugs tested in a urine drug screen and relevant clinical parameters

Drug	UDS time frame [1]	Metabolites	False positives	False negatives	Detection limit (ng/mL) [1]
Amphetamine	48 hours	Various, including MDMA	Pseudoephedrine Bupropion Ranitidine	ClO [5] Peroxides [5] PCC	500
Cocaine	2–4 days	Benzoylecgonine	Topical anesthetics	Excess hydration [5]	150
Marijuana (single use)	5–7 days for single use, or up to 45–60 days for chronic use	11-nor-9-carboxy-THC	Efavirenz Dronabinol	Nabilone Excess hydration [5] Nitrites [5]	50

Table 42.1 (continued)

Drug	UDS time frame [1]	Metabolites	False positives	False negatives	Detection limit (ng/mL) [1]
Opioid	48 hours	Various, including codeine/morphine	Dextromethorphan Diphenhydramine Doxylamine	ClO	2000
Phencyclidine	8 days	Hydroxylated PCP	Diphenhydramine Ketamine Lamotrigine MDPV Tramadol Venlafaxine		25
Tricyclic antidepressants	5 days	Nortriptyline	Seroquel Trileptal Benadryl Flexeril Thioridazine Thorazine		300

ClO hypochlorite, *PCC* pyridium chlorochromate

To counteract adulteration of UDS, laboratories have devised multiple methods. A urine integrity test can assess temperature, pH, specific gravity, and creatinine of a sample and compare it to normal values [5]. Color tests can detect whether certain contaminants are present; however, these tests may result in false positive tests [5].

False positive results have significant implications on a patient's treatment or employment. Positive screens on EIA can be attributed to similar structures, but cross-reactivity is observed in compounds that do not necessarily share similar structures.

Lastly, careful consideration of opiate metabolites must be taken into account to help determine chronicity and type of opiate use. As shown in Table 42.2, hydrocodone and hydromorphone metabolites are seen in patients with chronic opiate regimens. Therefore, those persons who recently started codeine or morphine medications may be suspected of taking diverted opiates if their UDS reveals evidence of hydrocodone and hydromorphone metabolites, respectively. Similarly, those persons taking chronic morphine may be produce all the conventional morphine metabolites—however, should be suspected of heroin use if their UDS reveals all these metabolites with the new emergence of 6-monoacetylmorphine metabolite.

42.5 Management Considerations

Repeat UDS testing may be useful to increase the likelihood of true positives and negatives. Because UDS testing is not confirmatory, a second test that produces the same result as the first may prove to be surrogate for confirmative testing and can help with clinical decision-making. A repeat test, especially if random or unannounced, can greatly decrease the chance of urine sample adulteration, dilution, or substitution.

Table 42.2 Opiate specific metabolites

Drug	Controlled substance schedule category	Metabolites	Notes
Heroin	1	6MAM → Morphine[a]	[a]Morphine → Hydromorphone in persons with chronic opiate use
Fentanyl	2	Norfentanyl	
Methadone	2	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP)	
Hydromorphone	2	Norhydromorphone Nordihydroisomorphone	
Hydrocodone	2	Hydromorphone Dihydrocodeine Norhydrocodone[b]	[b]Norhydrocodone → Norhydromorphone
Oxycodone	2	Oxymorphone Hydrocodone	
Morphine	2	Hydromorphone[c,d]	[c]Seen in persons with chronic opiate use [d]Hydromorphone → Norhydromorphone and Nordihydroisomorphone
Codeine	3	Hydrocodone[c,e] Morphine[a] Norcodeine	[c]Seen in persons with chronic opiate use [e]Hydrocodone → Hydromorphone [a]Morphine → Hydromorphone in persons with chronic opiate use

In the outpatient setting, UDS testing can be helpful to screen for substance use disorders and to assess for medication adherence. Many clinics have point-of-care testing (POCT) and can quickly produce a result from a UDS. However, much like in the inpatient setting, POCT is vulnerable to false positive and false negative results and requires confirmatory testing, which can take several days to return. In the outpatient setting, confirmatory testing may be worth pursuing given the lack of urgency in clinical decision making and the chronicity of patients with chronic pain syndromes.

42.6 Summary

Indications for obtaining UDS:

- Suspected illicit drug use or substance use disorders based on clinical context
- Ensuring compliance to prescribed drug use
- Federally mandated for employers or courts
- Assessing medication adherence

Drugs and metabolites:
- Different drugs have their own UDS time frame and detection limit, which affects their results on a UDS, depending on the parameters
- Some drugs have multiple metabolites, which can complicate the interpretation of UDS testing and requires careful, judicious analysis

False positives and negatives:
- Because drugs may have multiple metabolites, and certain medications can sometimes cross-react, false positive rates can be considerable
- There are many ways to falsify a UDS, including the dilution, substitution, and adulteration of urine
- Laboratories have improved their ability to detect false specimens, but there is still much to be improved

Management considerations:
- Early UDS administration can help to screen for drug abuse or drug diversion, both of which can impact clinical care and prescribing patterns
- Depending on the detection limit set by a certain laboratory, the same value could be interpreted as either positive or negative
- Given the frequency of false results, clinicians must use the results from a UDS within clinical context and consider confirmatory testing if appropriate

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Correction to: Patient with Renal Failure

Raj Desai and Nalini Sehgal

Correction to: A. Abd-Elsayed (ed.), *Guide to the Inpatient Pain Consult*, https://doi.org/10.1007/978-3-030-40449-9_10

Two errors have been corrected as follows on page 128:

Error in sentence:
Avoid codeine, morphine, meperidine, dextropropoxyphene and pethidine in CKD
Correction in sentence:
Meperidine has been removed from this sentence

Error in sentence:
Start with Acetaminophen <4 g/daily (2 g if concomitant renal failure)
Correction in sentence:
Concomitant renal failure has been replaced with *concomitant hepatic failure*

The updated version of this chapter can be found at https://doi.org/10.1007/978-3-030-40449-9_10

A. Abd-Elsayed (ed.), *Guide to the Inpatient Pain Consult*,
https://doi.org/10.1007/978-3-030-40449-9_43

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A. Abd-Elsayed (ed.), *Guide to the Inpatient Pain Consult*,
https://doi.org/10.1007/978-3-030-40449-9