Perioperative Psychiatry

A Guide to Behavioral Healthcare for the Surgical Patient

Paula C. Zimbrean
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To Silvia, Adrian, and Moni, whose unrelenting encouragements made this project, and so much more, possible. PZ

To papa, for Super Soaker skirmishes, steady wisdom, and gifting me with your love of life and learning. MO

To Christine, my better half, whose love and support allowed me to pursue higher goals in my career. Without her, I would not be who and what I am today. HBL

Foreword

In this book, *Perioperative Psychiatry*, Drs. Zimbrean, Oldham, and Lee have spelled out a compelling argument that team-based care for the surgical patient results in improved quality, enhanced safety, and better outcomes. While traditional models of surgical care have focused on the pathophysiology of surgical disease, the bio-psycho-social model of clinical medicine (developed and pioneered by Drs. George Engel and John Romano at the University of Rochester several decades ago) is embedded in the DNA of the institution where I serve as Chair of the Department of Surgery. The complex interactions of biological, psychological, and social factors all need to be considered and addressed to make the surgical patient well, and a singular focus on biology or pathophysiology is outdated, misguided, and ineffective. *Perioperative Psychiatry* provides a clinical roadmap for the bio-psycho-social model of surgical care.

In surgery, embedded psychiatrists, as part of our teams, have become increasingly common. For example, our live-donor liver transplant program operates as a multidisciplinary unit where a thorough preoperative psychiatric evaluation is required, and perioperative and often long-term psychiatric care are provided to both the donor and recipient to optimize results. Psychiatrists and behavioral health professionals play a critical role, and their input is necessary in any high-performing transplant program. Similarly, in our end-stage heart failure program, decisions about who is eligible for a left ventricular assist device (LVAD) require a thorough psychiatric evaluation and preoperative screening for untreated or undertreated psychiatric or behavioral health illnesses. Rather than view psychiatric disease as a disqualifier for these complex life-saving procedures, we feel that proactive diagnosis and ongoing treatment of these illnesses will make more patients eligible and sustain benefit from LVAD surgery and maintenance.

While in many areas these interprofessional teams are well established, we certainly could do better, and this textbook provides a detailed, comprehensive, and practical blueprint for developing high-performance partnerships between surgeons and behavioral health professionals to enhance patient care and improve outcomes. As Professor Lee correctly points out in the Introduction, surgeons tend to underestimate the prevalence of psychiatric illness in their patients, and even when recognized, access to a consultation-liaison psychiatrist is often limited or nonexistent. It is my hope that this textbook stimulates progress in what I consider to be a glaring unmet need among surgery patients, even decades after Engel and Romano showed us that a comprehensive, team-based approach to the whole patient is what it takes for optimal healing.

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1 Introduction

Hochang Benjamin Lee

During an episode of the *TED Radio Hour*, Atul Gawande, M.D., Harvard surgeon and famed author of *The Checklist Manifesto*, was once asked what the biggest problem in our healthcare system was. The soon-to-be-appointed CEO of the Amazon-Berkshire-JPMorgan health venture had a ready answer:

> *We are trained, rewarded and hired to be cowboys. And what the individual clinician says is what goes. We're neither trained, rewarded nor hired to be members of teams.* [1]

In my experience as a consulting psychiatrist to surgeons, with few exceptions, I have known surgeons to be consummate team players who work closely and intensely with the members of their multidisciplinary surgical team including anesthesiologists, certified registered nurse anesthetists, OR and circulating nurses, and surgical technicians. External to their surgical team, however, surgeons also have a strong sense of clinical insularity, and this can create challenges to collaborating with behavioral specialists and to providing cost-effective, quality care to patients with complex behavioral health needs. To meet this challenge, I hope this book introduces a new member to the surgical team: a psychiatrist.

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In a value-based, person-centered healthcare culture, the behavioral health service needs of surgical patients have become increasingly important. Estimates of the prevalence of psychiatric problems in surgical patient approach 50% [2] and effective management of psychiatric comorbidities during pre-, peri-, and postoperative care have been shown to have a substantial impact by reducing length of stay, readmission rates, and adverse outcomes including mortality [3–6]. During my own career as a consultation-liaison (CL) psychiatrist, I have seen this transition in process. Management of behavioral issues has become central to several surgical service lines, and I have watched the increasing number of surgeons and behavioral health specialists working side by side in multidisciplinary clinical teams (e.g., transplantation surgery and bariatric surgery).

Nevertheless, the bulk of clinical interaction between surgery and psychiatry occurs through requests to CL psychiatrists in response to acute psychiatric issues that have become a barrier to surgical care delivery. In general, most psychiatric consultation requests are placed under one of the following five conditions:

1. Capacity assessment is needed because the patient cannot provide informed consent for a medically necessary procedure related to cognitive impairment or psychiatric symptoms.
2. Proactive psychiatric evaluation and intervention are requested because previously known

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psychiatric conditions have a potential to compromise surgery, recovery, or outcomes.

3. Advice for the maintenance or adjustment of psychotropic medication is needed to avoid potential complications during anesthesia, or surgery due to drug-drug interaction or medication for surgical care could complicate psychiatric care.
4. Surgical team needs assistance in evaluation and treatment of new-onset psychiatric symptoms or acute exacerbation of existing psychiatric conditions due to the stress of surgery.
5. Communication strategies and behavioral plans are requested as the surgical care faces challenge in caring for patient with personality disorder and difficult behavior.

This conventional "consultation model," though, works best when surgeons can reliably identify emerging psychiatric issues *before* reaching a crisis level and the consulting psychiatrist has expertise and familiarity with common psychiatric issues presenting in surgical patients. However, neither of these can be assumed as psychiatry and surgery often seem to be at the opposite ends of the spectrum in their approach to healthcare. For example, a recent *NY Times* article was entitled, "Your Surgeon Is Probably a Republican, Your Psychiatrist Probably a Democrat" based on a data that suggested diverging political ideology that might affect treatment recommendations across various specialties [7, 8].

Surgeons tend to underestimate the frequency of psychiatric disorders in their patients even more than other physicians do, and they are less likely to refer patients to psychiatrists than are other physicians [9]. On the other hand, except in larger academic medical centers staffed by CL psychiatrists, it is rare to find psychiatrists who are familiar with the perioperative issues of rapidly advancing surgical care. According to the American Hospital Association, community and rural hospitals represent 85% of all hospitals and serve populations without access to or neglected by larger hospitals and healthcare systems [10]. In these smaller hospitals without a CL psychiatrist, a surgeon requesting consultation from an available behavioral health specialist may be skeptical about the recommendations being offered—and often justifiably so.

With this book *Perioperative Psychiatry*, we aim to bridge this glaring gap in clinical care by describing psychiatric issues commonly encountered in surgical patients. In fact, we hope the content will be helpful for trainees and seasoned practitioners, both in surgery and psychiatry. To address the practical issues in evaluation and management of psychiatric issues among surgery patients, we organized this book in two parts. Part I deals with common psychiatric issues that occur across surgical settings: (1) capacity assessment in consent process, (2) postsurgical delirium, (3) psychopharmacological issues related to anesthesia, (4) psychiatric aspects of perioperative pain management, and (5) the role of psychological assessment and therapy in the perioperative period. Part II focuses on psychiatric issues in select surgical populations: (1) cardiothoracic surgery, (2) noncardiac thoracic or pulmonary surgery, (3) neurosurgery, (4) transplantation surgery, (5) bariatric surgery, (6) aesthetic/cosmetic surgery, (7) obstetric and gynecological surgery, and (8) pediatric surgery. By covering general topics in depth in Part I, we provide detailed, up-to-date knowledge for interested trainees and practicing clinicians. In Part II, we provide an accessible reference and guide for the psychiatric approach to specific surgical populations.

"There is no health without mental health," proclaimed our former surgeon general, David Satcher [11]. Nor is there mental health without physical health. As members of a multidisciplinary surgical service line, surgeons and psychiatrists may approach the same patient from different perspectives, but ultimately they have a common goal: achieving maximum health through cost-effective delivery of surgical care. With the advent of value-based healthcare, *Perioperative Psychiatry* expounds on the necessity of a biopsychosocial approach to surgery in which team-based care provides personalized medicine. From the start of my career as a CL psychiatrist, I have enjoyed the camaraderie and generosity of countless surgeons who patiently taught me about the intricacies of surgical care. In this same collaborative spirit, I hope this book facilitates and enhances teamwork between surgeons and psychiatrists in care of surgical patients with behavioral health service needs.

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Part I

General Concepts in Perioperative Psychiatry

2 The Role of the Psychiatrist in the Perioperative Setting

Paula C. Zimbrean

Brief History of Psychiatric Consultation in the General Hospital

Consultation-liaison psychiatry (CLP) is the subspecialty of psychiatry that provides clinical service, teaching, and research in nonpsychiatric health-care settings [1]. CLP intersects with psychosomatic medicine, a broader multidisciplinary field that focuses on the emphasis of the role of psychological factors upon one's health [2]. The first psychiatric consultation-liaison (CL) service in a general hospital opened at Albany Hospital in New York in 1902. It took over a decade until the next similar service was established, at John Hopkins Hospital, in Maryland [3]. The practice of CLP grew steadily over the following decades, and by the early 1990s, over 900 CLP programs were reported functional [1]. Interestingly, in 1929, Henry offered the following guidelines to inform the psychiatrist who wished to work with other physicians: careful observation is more acceptable than inspired guess work, communication should be free of jargon, and there must be flexibility in the application of theory and the choice of therapy [4]. These principles are still standing now, almost 90 years later.

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While the framework for consultation psychiatry was accepted relatively quickly, debate surrounded the liaison task of the psychiatrist working in the general hospital setting [5]. Very early it became obvious that to address psychiatric problems in the general hospital setting, the consultant psychiatrist had to spend significant amount of time educating family and medical staff about the nature of psychiatric illness and/or the treatment recommended. This led to the service model of psychiatrists becoming embedded within medical or surgical units, joining medical rounds, or helping medical staff interact with psychiatric patients. In an era when psychoanalytic theory and practice dominated the field of psychiatry, the liaison work even included *countertransference rounds* on the intensive care unit, during which medical staff was encouraged to process their own emotions raised by taking care of terminal or difficult patients [6]. As the biopsychosocial model gained acceptance and managed care systems encouraged the use of time-limited interventions, CLP shifted from the predominant use of psychodynamic clinical tools to an emphasis on biological and behavioral interventions. CLP started to expand on specialty services such as hemodialysis [7] and OB-GYN [8] or in general outpatient clinics [5]. All these developments led to the pursuit of subspecialty status within the American Board of Medical Specialties (ABMS), a process fraught with challenges as detailed recently by Boland [9].

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The Impact of Psychiatric Symptoms on Postsurgical Outcomes

A broad range of evidence suggests that psychiatric comorbidities represent a risk factor for less desirable outcomes after different types of surgery. Many studies have evaluated the impact of psychiatric comorbidities as an independent risk factor; for instance, comorbid psychiatric disorders are associated with higher rates of complications following cervical spine surgery including infection, readmission, and revision surgery [10]. Preoperative psychiatric conditions have been linked with a higher risk of unfavorable discharge, neurological complications, venous thromboembolic events, and acute renal failure in patients who underwent surgical intervention for lumbar degenerative disc disease [11]. Prior psychiatric diagnosis has been associated with significantly higher risk of in-hospital mortality for trauma surgery patients, with higher risk of complications after trauma surgery and longer length of stay as shown in a systematic review published in 2017 [12]. Also, for patients undergoing appendectomy and laparoscopic cholecystectomy, a prior psychiatric disorder predicted longer time from symptom appearance to admission, longer hospitalization, and an increased rate of postoperative complications [13].

Other studies have assessed how specific psychiatric conditions or psychological factors impact various outcome measures after surgery. For instance, depression before peripheral artery disease diagnosis is associated with higher risk of amputation and higher risk of mortality after amputation [14]. Preoperative depressive symptoms influence patient's satisfaction with health care up to 2 years after surgery [15]. High cooperativeness as a personality trait was associated with better outcomes after bariatric surgery [16]. Cognitive distortions predisposed to higher pain after hand and upper extremity surgery [17].

The overall impact of chronic treatment with psychotropic medications upon surgery outcomes is still being investigated. A handful of studies has suggested a higher risk of postoperative complications in patients who regularly take certain psychotropic medications, for instance, a higher risk of respiratory depression in orthopedic interventions [18, 19] or higher postsurgical mortality in patients on anxiolytic medications [19]. Similarly, several studies have investigated the role of SSRIs in increasing bleeding risk in various types of surgery [20–22]. In each instance, the mechanism whereby a given psychotropic agent might confer medical risk should be considered and differentiated from the potential effect of the condition for which the psychotropic agent is being prescribed. For example, neuroleptics when used to manage the behavioral disturbances in delirium entail certain medical risks, but outcomes of those who receive neuroleptics for this purpose must be differentiated from similarly agitated and comparably ill patients who never receive such agents. On the other hand, psychotropic medications, including antidepressants and neuroleptics, may have unique benefits for the surgical patient *without* psychiatric illness by improving postoperative pain management [23, 24] and postoperative recovery [25].

Mental health problems should not be seen as a uniform predictor of poor outcomes. To the contrary, a recent report including prospectively collected data of 1473 knee surgeries found that patients with poor baseline mental health experienced greater relative improvement in their function after surgery despite reporting greater dissatisfaction [26]. Similarly, case reports suggest that certain patients with serious and persistent mental illness have favorable postsurgical outcomes, even after organ transplantation [27]. Interesting findings are also emerging from cosmetic surgery where some procedures have been reported to improve specific psychological and functional domains as will be discussed in Chap. 13.

Psychiatric Conditions Occurring in the Peri-surgical Setting

In addition to assisting with treatment of patients with pre-existing psychiatric illness in the perioperative setting, CL psychiatrists are often asked to evaluate and treat new conditions that occur in the context of surgery, either due to the direct physiological consequences of surgery or surgical illness or to psychological reactions to surgical care.

Depression. Multiple studies have indicated that postoperative depression is associated with delayed recovery and with more complications and even mortality. For CABG patients, depression increases postoperatively [28] and is associated with more complications [29] and longer hospitalizations [30]. Another example consists in patients with hip replacement with depression who tend to report worse pain, require higher doses of opioids [31] and have a higher readmission rate [32] compared with hip replacement patients without depression. The risk factors and the impact of postoperative depression vary by specific type of surgery and will be discussed in details in Chaps. 8, 9, 10, 11, 12, 13, 14, and 15.

Posttraumatic Stress Disorder Related to Surgery. In a sample of 93 head and neck cancer survivors, 33.4% had posttraumatic stress symptoms (PTSS), and 11.8% met the criteria for posttraumatic stress disorder (PTSD) [33]. In solid organ transplant recipients, approximately 15% of patients developed PTSS with the most important risk factor being pre-existing psychiatric morbidity, renal transplantation, and chronic benzodiazepine prescription [34]. In a prospective study of patients over 60 who underwent noncardiac surgery with general anesthesia, 12% had PTSD 3 months after surgery, and postoperative delirium and preoperative depression were identified as risk factors [35]. Anesthesia awareness is a specific risk factor for psychological sequelae, with up to 15% of such patients developing PTSD [36].

Substance Use. A recent retrospective cohort study of 6000 patients revealed that 62% had filled their opioid prescriptions 1 month after surgery and 22% did so 6 months after surgery. Among those who filled opioid prescriptions 2 months postsurgery, between 71% and 76% had also received opioid prescriptions prior to surgery. Orthopedic surgery, colorectal surgery, multiple procedures, and a prior history of opioid use were associated with long-term opioid use [37]. Another cohort study of over 30,000 patients who underwent minor and major surgery between 2013 and 2014 found a rate of new persistent opioid use between 5.8% and 6.5%. By way of comparison, though, the rate of persistent opioid use in a control nonoperative cohort was 0.4%. In this population, risk factors for opioid use after surgery included tobacco, alcohol, and substance use disorders as well as mood disorders, anxiety disorders, and perioperative pain disorders [38]. In an attempt to reduce the risk of chronic opioid use, guidelines have been developed to inform home postoperative pain regimens. One such guideline recommends that the amount of opioid use the day before discharge should indicate the number of all opioid pills that should be dispensed for home use [39]. Other authors have found that an enhanced recovery program after thoracic surgery reduces the need for opioids at discharge [40]. Identifying and addressing pre-existing psychiatric disorders or substance use disorder is likely to reduce the postoperative use of opioids; however, the impact of psychiatric consultation in this setting still needs to be investigated.

Postoperative Cognitive Impairment (PCI) or Postoperative Cognitive Dysfunction (POCD) Postoperative delirium typically presents 2–3 days after surgery; however, many patients develop postoperative cognitive impairment (PCI) in the acute postoperative setting that does not rise to the level of delirium diagnosis. Similarly, many patients with postoperative delirium or PCI develop lingering postoperative cognitive dysfunction (POCD) for weeks or even a few months after surgery. The precise causes and clinical course of various types of delirium continue to be a topic of keen interest to researchers. For instance, delirium associated with sedatives, hypoxia, and sepsis or “unclassified” delirium has been shown to predict worse cognitive function at 12 months, whereas metabolic delirium did not [41]. Similarly, delirium severity may also predict development of cognitive dysfunction as shown in a prospective study that followed postsurgical patients for 3 years after the surgical intervention [42]. Several anesthesia-related factors have been linked to later development of dementia including choice of anesthetic agent, the number of exposures to general anesthesia, the cumulative exposure time, and the organ involved in surgery [40]. Neural inflammation and oxidative stress secondary to anesthesia and surgery are considered two of the possible mechanisms for these persistent cognitive problems [43]. The impact of different surgery types on cognition should be studied individually because some surgeries, for instance, such as weight loss surgery, may even lead to cognitive improvement [44]. Twelve percent of patients over 65 who underwent surgery for removal of a solid tumor developed cognitive decline 3 months postsurgery. Executive function was the domain that declined the most [45]. Recent findings also suggest that dexmedetomidine can improve cognitive function in this situation [46]. A psychiatric evaluation can screen for persistent cognitive impairment and identify the need for further testing or additional rehabilitation or home services necessary to ensure good adherence after discharge.

Integrating the Psychiatric Consultation into the Surgical Service

In the general hospital, psychiatric comorbidity is associated with increased length of stay, higher medical costs, and increased rate of rehospitalization [47]; however, it is often underdiagnosed in surgical patients. Each chapter of this book will discuss in detail the prevalence of psychiatric problems among specific surgical populations. For example, a prospective study of surgical admissions at two separate institutions showed that 12.5% of patients had significant depression, 18.7% had significant anxiety, and an additional 8.3% had both depression and anxiety. About 22.3% of the cohort was judged to need a referral for psychiatric assessment [48]. A recent study found that while the rate for psychiatric consultations was 3.2% of the total admissions to a general hospital, for the surgical service, that rate was 26.1% [49].

The role of psychiatric consultation in a perioperative setting may involve any of a host of specific questions, but broadly these questions variously entail improving in-hospital patient care, collaborating with a patient regarding their interests, and optimizing outcomes. These goals are accomplished through accurate psychiatric diagnosis and development of a perioperative plan for psychiatric conditions, which may include medication changes or psychotherapeutic interventions. Psychiatrists often assist in the identification of treatment of behavior that interferes with safe, efficient care delivery or in the assessment of capacity of a patient to provide informed consent for surgery or other interventions. In addition, psychiatrists often assist in mental health referral when treatment in the hospital is completed. The consultant psychiatrist often collaborates with other clinicians who focus on specific aspects of the overall psychosocial care such as behavioral health psychologists (who focus on improving coping with illness, as illustrated in Chap. 7), addiction counselors (who provide early intervention for substance abuse [50]), and social workers (who may be involved in a variety of aspects of patient care from coping with illness to caregiver support).

Models of Psychiatric Consultation in the General Hospital

The traditional psychiatric consultation begins with a request for consultation from the primary team. The psychiatrist then clarifies the questions that need to be addressed with the consultee, reviews the chart, interviews the patient and the family, obtains collateral information from outpatient providers as needed, and provides a written consultation report to the primary team. Depending on the setting, the psychiatrist may be involved in the implementation of the treatment recommendations or assist the primary team in doing so (e.g., sometimes consultants order the psychotropic medications or imaging tests themselves, while on other settings, the orders are placed by the primary team).

The "embedded" psychiatry consultation model was briefly described above. It consists of a psychiatrist participating in rounds with the primary hospital team, providing consultation promptly, and being available for immediate assistance if questions about management of psychiatric or behavioral issues arise. In this model, psychiatric intervention is still provided "upon request" or "reactively"; however, the psychiatrist can spend more time on liaison work.

Recently, proactive consultation models have been developed in which all admissions to a general hospital are screened for mental health conditions and psychiatric consultation is provided promptly in an ongoing discussion with primary medical and surgical teams [51]. Other proactive consultation service models may screen for a specific psychiatric problem (e.g., depression post CABG). For organ transplantation and bariatric surgery, the psychiatrist is involved in the assessment and care of surgical patients long before surgery and plays a formative role in candidate selection, as will be discussed in Chaps. 11 and 12.

Impact of Psychiatric Consultation for Surgical Patient upon Health-Care Cost

Assessing the effectiveness of a psychiatric consultation service in the general hospital is challenging in many ways. Foremost, the complexity of surgical patients and the care they receive makes data interpretation difficult due to the range of confounding factors and the various interactions among these. In addition, defining the outcomes of the psychiatric consultation is challenging: some authors emphasize symptoms improvement, which itself can be assessed subjectively by the patient or objectively by medical staff or by mental health-trained clinicians. Others focus on patient satisfaction, consultee satisfaction, or administrative outcome such as length of stay or reduction of health-care cost. A systematic review of the studies assessing the impact of a psychiatric consultation service found that multiple programs had a positive impact [52]. It is an interesting note that one of the first studies to investigate the financial impact of psychiatric consultation was performed on orthopedic surgical units and showed that prompt psychiatric consultation significantly reduced postoperative length of hospital stay [53]. Administrators may be encouraged, too, that psychiatric consultation can also increase hospital payments when adjusted for length of stay in bundled care settings [54].

Whether specific therapeutic interventions mitigate the impact of psychiatric factors on postsurgical outcomes is only beginning to be studied. For example, a ten-session psychological intervention based on cognitive behavioral therapy found that surgical candidates for knee osteoarthritis had improved mood, pain control, and physical function 6 months after surgery [55]. However, a recent systematic review found no evidence that psychological treatments improve mortality, risk of revascularization, rate of repeated myocardial infarction, or rate of cardiac mortality among coronary heart disease patients [56].

Proactive psychiatric consultation services have been reported to reduce length of stay on inpatient medical units [51, 57], and timely psychiatric evaluation has been associated with a 33% reduction in cost of constant observation among general medical inpatients [58]. However, to date such proactive models have not been studied among surgical services.

Conclusions and Future Directions

Several decades of collaboration between psychiatry consultants and surgical services suggest that promptly addressing psychiatric conditions leads to better clinical outcomes and facilitates overall patient care for primary surgical teams. As life expectancy increases and both surgical and psychiatric treatments improve and become more widely accessible, a growing number of patients with psychiatric comorbidities will receive surgical care, so the demand for psychiatric assessment and management in the surgical setting is expected to grow. General health concerns such as the opioid crisis will impact guidelines for postsurgery follow-up, and as such, early identification and treatment of substance use disorders in this setting will become essential. The challenges of optimizing the mental health of candidates before non-urgent, non-life-threatening, non-curative surgeries such as cosmetics, gender reassignment surgeries, or vascularized composite allografts (e.g., face transplant) will become increasingly paramount, especially where quality of life—rather than survival—is the main outcome measure. Prospective studies on specific psychiatric complications related to surgery (such as persistent cognitive impairment) may lead to valuable insights into mechanisms of cognition and possible treatments. These are just a few examples of possible directions of inquiry. We hope this volume will provide a rich knowledge base for those interested in advancing the clinical and research interface between psychiatry and surgery.

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3

Consenting to Surgery: Assessing the Patient's Capacity to Make Decisions About Own Medical Care

Maya Prabhu

Introduction

Informed consent is an ethical and legal doctrine at the heart of shared medical decision-making in the USA. Informed consent requires that physicians disclose potential interventions, their risks and benefits, and any alternatives to the proposed treatment so that patients are empowered to make informed decisions about their health. Whereas obtaining informed consent is standard of care and codified in state and federal laws and regulations, its successful execution in clinical practice can be elusive. The circumstances under which physicians must discuss difficult therapeutic options with patients are frequently fraught with layers of complexity. The identification of the risks of greatest relevance to the patient is determined both objectively and subjectively. Even after a patient gives consent, patients and their family may report failing to retain or understand the information they were provided [1].

This clinically oriented chapter will provide an overview of some informed consent challenges in surgical care, the role of the consultation psychiatrist in assisting with capacity assessments if necessary, and several select issues relating to the informed consent process in the perioperative setting with adult patients. Overall, obtaining informed consent ought to be conceptualized not as a single discussion or a signed legal consent form but as an iterative process that yields a mutual understanding between physician and patient about the goals and expectations for care.

A Brief History of Informed Consent

From an ethical perspective, informed consent is grounded in the principles of individual autonomy and the patient's right to self-determination. From a legal perspective, informed consent analysis has evolved from the tort of battery (the intentional touching of a person in a harmful or offensive manner without their consent) to claims in negligence. Currently, US courts tend to characterize claims as battery when they arise from fact patterns where a physician performs procedures without permission, whereas claims based on the lack of disclosure may be considered under malpractice or negligence theory.

The legal history of informed consent is of particular importance to surgical practitioners since significant early litigation arose from surgical cases. The landmark case that established the principle of informed consent in US law occurred in 1914, *Mary E. Schloendorff* v. *The Society of the New York Hospital*; in that matter, the patient was subject to surgical management of a fibroid [2]. The patient, who had agreed to undergo

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anesthesia for examination, but refused surgery, suffered a brachial plexus injury that led to the amputation of fingers on one hand. The patient argued that she had not consented to the procedure and that she would not have been injured if her wishes to avoid surgery had been followed. The court concluded that the operation amounted to "medical battery." Justice Benjamin Cardozo writes on behalf of the court: "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. This is true except in cases of emergency where the patient is unconscious and where it is necessary to operate before consent can be obtained" [2].

The importance of full disclosure was further underscored in 1960 in the case of *Natanson* v. *Kline*; in this scenario, the physician did not tell the patient about the risk of burns from cobalt radiation for breast cancer [3]. The court found that if injury results from a known risk that is not disclosed to the patient, the physician may be liable. The case also came to be understood as codifying the so-called professional standard in which the information to be conveyed was left to the discretion of the physician and community practice rather than what a patient might wish to know.

A third milestone case in 1972 further expanded the scope of the physician's communications to the patient and shifted the framework to what a "reasonable patient" would want to know. In *Canterbury* v. *Spence*, the patient who had undergone a laminectomy became paralyzed as a result of a postoperative fall. The court determined that the risk of possible paralysis should have been disclosed. In an oft-quoted rationale by Justice Robinson, "respect for the patient's right of self-determination on particular therapy demands a standard set by law for physicians rather than one which physicians may or may not impose on themselves" [4]. At the current time, approximately half of the US state statutes endorse a "reasonable patient" standard and the remaining a "reasonable physician" standard [5, 6]. However the standards to which clinicians are held are shaped not only by their state's statutory language but developing case law that may introduce additional nuances. While larger medical institutions and clinics are likely to be kept abreast of legal developments by their counsel offices, smaller practice groups and solo practitioners ought to be proactive by regularly reviewing policies, procedures, and documentation related to how informed consent is obtained.

Overview of the Informed Consent Process

Imparting Relevant Information

Informed consent is defined by the Joint Commission as "an agreement or permission accompanied by full notice about the care, treatment, or service that is the subject of the consent. A patient must be apprised of the nature, risks, and alternatives of a medical procedure or treatment before the physician or other health care professional begins any such course. After receiving this information, the patient then either consents to or refuses such a procedure or treatment" [7]. A more succinct description familiar to psychiatrists was put forth by Appelbaum, "a process by which the treating health care provider discloses appropriate information to a competent patient so that the patient may make a voluntary choice to accept or refuse treatment" [8].

Informed consent can be construed therefore as having the following elements:

1. Disclosure (the patient has been provided relevant information)
2. Voluntariness (the decision is free of undue influence or coercion)
3. Understanding (the patient can appreciate the risks, benefits, and nature of the procedure)
4. Capacity (the patient has the ability to engage in rational deliberation) [8, 9].

The first element, disclosure, is typically done by the treating surgical team which has the best understanding of the medical condition, treatment options, and familiarity with the patient [8]. Much of the academic literature on obtaining informed consent in the perioperative setting focuses on the content of the information which patients ought to understand prior to agreeing to treatment (see, e.g., Fedson et al. [10]). However, no single standard protocol for informed consent will suit all procedures and all patients. Numerous regulatory agencies provide general guidelines on the minimal information to be conveyed, particularly on disclosure forms, including the Joint Commission, Centers for Medicare and Medicaid Services, and American Medical Association [11, 12]. Physicians are encouraged to refer to informed consent guidelines provided by their subspecialty organizations (such as the one by the American Academy of Ophthalmology [13] or the website for the American College of Surgeons recommended templates) for forms and discussion which can be tailored to specific surgical routines to help ensure compliance with accreditation and regulatory requirements [14].

Discussions with patients about informed consent often focus on the risk magnitude to guide what patients might consider material or relevant [15]. However, there is ample evidence that in postoperative assessments of patients' memory of complications and risks, there were significant deficits in understanding and recall of those risks [16, 17]. Clinicians' tendency to provide supplemental information to alleviate confusion may in fact create uncertainty and informational overload rather than clarity [18]. This gap between what information has been *provided* and what information the patient *originally understood as relevant* to themselves may partially account for patients' retrospective feeling that they were not informed of salient facts, even when they were so advised.

One study of this incongruence between pre-procedure satisfaction with the information provided and the post-procedure dissatisfaction suggests that, whereas data about treatment theories and protocols can be satisfactorily communicated, the actual patient experience of discomfort or suffering at the time they are receiving information often seriously compromises a patient's ability to understand and retain this information [19]. A successful informed consent process therefore anticipates and addresses patients' emotional needs as well as their cognitive needs. "While being informed was not considered unimportant by the patients, and while in their own view, they become well informed during the pre-treatment phase, the consent process served primarily to establish trust with physician and staff. Trust was built during the process of information –sharing and on the opportunity for the subjects to express and have addressed their fears, concerns and questions. The trust they felt in turn help them maintain hope for a positive outcome" [1]. Seen in this light, the informed consent process can be a therapeutic intervention not just an ethical or legal imperative [20].

Finally in this "informational" stage of the informed consent discussion, expectations about follow-up care, including necessary adherence to specific medication regimens and the changes in postoperative lifestyle, may also be crucial to the conversation and assessment of patient's understanding of the proposed treatment. The patient's ability to follow post-surgery recommendations may also be germane to an assessment of an understanding of treatment.

Enhancing the Informed Consent Process

Physicians need not shy away from actively educating their patients to help them attain understanding. This may involve reviewing critical information over multiple discussions or engaging with the patient's identified supports (family, friends, clergy). The informed consent process requires an individualized approach tailored to a patient's level of education and understanding. Many authors have encouraged the use of learning aids to create "enhanced informed consent—designed to improve patient-surgeon communication, improve patient comprehension of the operative procedure, and protect the surgeon from medical malpractice claims" [5]. For example, preoperative marking photos could be signed by both patient and physician and included in the medical record. "This provides an unparalleled, living representation of the informed consent discussion… These photographs can be revisited if the patient reports concerns regarding the presence of postoperative scars, malalignment, asymmetries, or other differences" [5].

Studies "have confirmed the effectiveness of video and multimedia presentations in presenting information regarding knee arthroscopy, ankle fracture surgery, colonoscopy, and thyroidectomy" [21]. A 2016 study illustrated that the use of multimedia (e.g., videos of surgical procedures, computer animation, and graphics) enhanced the consent process, allowed patients to remember more information, and reduced the difference in the amount of information assimilated by patients with different levels of education [22]. Innovative technological tools whether they be on apps on smartphones or software with dynamic interfaces which are being developed for research informed consent processes could be used in the clinical realm as well [23]. Wollinger notes that elderly patients particularly benefited from the use of a multimedia presentation [24].

Psychiatric Referrals to Assess Capacity

It is often in this first disclosure stage that mental health concerns may arise requiring additional evaluation. Every adult patient is legally assumed to be capable of making informed medical care decisions, unless they indicate otherwise. And "even when there is no reason to anticipate need for a formal court proceeding, a clinician is expected to consider a patient's decisional capacity" [25] .

Frankly evident psychiatric symptoms such as depression, delusions, or cognitive deficits may impact patient's participation in a discussion, retention of critical information, or a realistic understanding of what quality of life will be after surgery. Patients with a previously diagnosed serious psychiatric illness such as schizophrenia may trigger a capacity consult, sometimes out of beneficent concern to protect vulnerable patients but sometimes based on the incorrect belief that all people with mental illness have reduced ability to provide consent [26]. While declining care, per se, ought not reflexively prompt a psychiatric consultation for capacity, very often it does. However, the same rights and considerations which allow patients to make informed decisions about their care and treatment also allow them to refuse care. Patients may also change their minds and withdraw consent for treatment they have previously authorized, even when the treatment has already been started. Regardless, the provider should document the decision in the patient's health record. At this point, a surgical team may seek recommendations from a consultation psychiatrist for a comprehensive assessment of capacity.

Though the two are often conflated, there are distinctions between the terms "competency" and "capacity." "Competence" is a legal term of art, rather than a medical one, and "refers to the degree of mental soundness necessary to make decisions about a specific issue" [27]. By contrast, the term capacity "is used by clinicians or other professionals to describe whether an individual can perform a specific task, be it the ability to drive or live independently or to consent to health care or change a will" [28].

In other words, a determination about competency reflects the outcome of a legal adjudication, whereas an opinion about capacity reflects the assessment of an evaluating physician. Consulting psychiatrists are often asked for a "competency evaluation" even when no legal adjudication is foreseen. In that situation, the consulting psychiatrist should clarify that the request is about the patient's ability to make a particular medical decision and identify the specific behaviors or statements that led to the consult.

Psychiatrists who assess patients' capacity to give informed consent should be aware of the informative content provided to the patient and of any particular clinical findings of the surgical team pertinent to this process [29]. Very often the focus of the psychiatric assessment is on voluntariness and capacity. The framework outlined by Appelbaum and Grisso in 1988 for assessing decision-making capacity continues to be the most widely used clinical standard [8]:

(a) The ability to communicate a choice
(b) The ability to understand the relevant information
(c) The ability to appreciate a situation and its consequences
(d) The ability to reason rationally.

Capacity is best assessed by a clinical interview and examination in which the physician explores each of the four decision-making abilities listed above and determines if there is any condition present that interferes with them and which might be remediated. Evaluation information should be combined with data provided by the primary team, knowledge from the family if available, previously articulated wishes, as well as the risks and benefits of the treatment themselves to ascertain whether capacity is intact.

Several instruments have been developed to aid the assessment of capacity, though they are not routinely used in the treatment context. Two of the more clinically oriented tools include:

(a) The MacArthur Competence Assessment Tool for Treatment (MacCAT-T), which provides structured questions to guide the interview and takes approximately 15–20 min to administer. The MacCAT-T is not in the public domain [30].
(b) The Assessment of Capacity for Everyday Decisions (ACED), which also uses a semi-structured interview format to assess the four decision-making domains [31].

Other tools include the Aid to Capacity Evaluation (ACE), the Capacity to Consent to Treatment Interview (CCTI), the Hopkins Competency Assessment Test (HCAT), and the Understanding Treatment Disclosure (UTD).

Often screening tools for cognition such as the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA) are used in the assessment of decisional capacity. Certainly, while dementia and delirium have been associated with impaired capacity, they are not synonymous with it [25] [please see Chap. 4 for further discussion of delirium]. Similarly, while incapacity is common in serious psychiatric illness, mere diagnoses alone do not imply incapacity [32].

Just as the primary surgical team may engage in an enhanced informed consent procedure to overcome impediments to understanding, so a consulting psychiatrist may also use creative ways to allow the patient to communicate their wishes despite physical impediments. Writing pads or boards, alphabet boards, and electronic tablets can lead to a better assessment of patient's capacity. Mechanical devices such as glasses, dentures, and hearing aids also amplify abilities. Bester et al. recently described how patients "overwhelmed by the illness experience and by the implications and complexity of decisions" may find their ability to make decisions taxed; this builds on Appelbaum's observations that fear and anxiety can interfere with a patient's ability to attend to and process information [8, 33]. Bester recommends "extending the decisional time frame, delivering news in a skillful and incremental way and using decision aids…to ensure the integrity of the informed consent process by protecting patients" [33].

When consulted to evaluate a patient's capacity to provide informed consent, a psychiatrist may give special attention not only to capacity but voluntariness of a patient's choice. Elderly patients, for example, can be particularly vulnerable in the informed consent process. Social factors, such as physical dependency, financial strains, and family pressures can prevent elderly patients from expressing truly autonomous decisions [34]. The consultant can also comment on relevant interpersonal dynamics, a patient's psychological strengths and weakness and likelihood for medical adherence that are pertinent in assessing voluntariness as well as capacity [35].

Capacity issues specific to psychiatric disorders:

1. Patients with depression: Major depressive disorder may particularly distort the "appreciation" component of the capacity assessment if depressed patients minimize the importance of the future possibilities which treatment might afford [36]. Symptoms of depression such as anhedonia (loss of the

ability to feel pleasure) may make it impossible for a patient to imagine a life worth living for; guilt and frank suicidality may cause a patient to believe that their suffering or death is deserved. Additionally, while depression is treatable, it may be seen by the primary team as "understandable" or "rational" in the context of a severe illness, as such capacity evaluators may underestimate the rigidity of the depressed person's thought process and the difficulties he or she may have in thinking through alternatives [37].

2. Patients with mania: Patients in the throes of a manic episode can exhibit a range of symptoms including boundless energy, grandiosity, and lack of inhibition or reckless behaviors; at times these are accompanied by paranoia, delusional thinking, and agitation. Perhaps more than other psychiatric patients, manic patients may demonstrate fluctuating or variable degrees or insight, understanding which negates the "consistent" expression of a choice [38]. The elevated mood of mania can contribute to a personal sense of invulnerability which distorts the "risk-benefit" analysis; and agitation and restlessness can contribute to difficulties with applying the information to their own situation or recalling information provided. If a patient is floridly psychotic, he or she may entirely dismiss the idea that they even have an illness that requires treatment or have bizarre beliefs which intrude upon the decision-making process.
3. Patients with obsessive-compulsive disorder: Patients with OCD experience intrusive thoughts or feel compelled to spend time in variety of behaviors or rituals such as cleaning and counting. There is relatively little written about how OCD can impact the informed consent process, but it's worth noting that OCD is one of the few diagnoses within the diagnostic manual that has a specifier that comments on insight. As with severe mood or psychotic disorders, individuals with OCD may experience thought rigidity and distortions and fail to incorporate important information to their understanding of their situation.
4. Patients with pre-existing cognitive impairment (e.g., mental retardation): Teams working with patients with an intellectual disability are likely to have to engage in a shared decision process involving the patient and someone like guardian, surrogate, formal caregiver, or family member. As a result, these patients are particularly vulnerable to having decisions made for them because of the assumption that they may not be able to make decisions for themselves or not having their wishes incorporated by the surrogate [39]. Communicating with persons with a disability may be particularly challenging, and they may require additional time, multiple explanations, and more creative modalities to explain the range of choices.
5. Patients with delirium: Delirium, which is characterized by changes in cognition and consciousness, is highly prevalent in a surgical population (see Chap. 4) with hypoactive delirium in particular going undetected. The very fluctuations in cognitive status which define delirium can impact each element of capacity including consistency of expressed wishes, understanding and recollection of the information provided, and an appreciation of their own situation.

Substituted Decision-Making

Surrogates for Medical Decisions

If a patient is found to lack decision-making capacity, the surgical team will need to rely on a surrogate or substituted decision-maker. There are multiple mechanisms for this including patient-appointed mechanisms (healthcare agent or proxy via a Durable Power of Attorney for Health Care) or court-appointed mechanisms (guardian or conservator).

Ideally, a substituted decision-maker would have been identified in advance by the patient with the confirming advance directive, or legal paperwork, readily accessible in the patient's chart. The Patient Self-Determination Act of 1990 requires that all patients who enter a US healthcare institution be asked about prior advance healthcare directives and that if a patient has none, they be provided information about them [40]. Surgical teams should also be aware that many state statutes render advance directives inapplicable if a woman is pregnant [41].

In the absence of prior arrangements, patients who have been found without medical decision-making capacity should be asked whom they would like to make decisions on their behalf. Because capacity is best thought of as being on a sliding scale and decision-specific rather than global, patients may still retain the ability to select who they would want to speak for them, even if they cannot engage in high-risk complex treatment choices [8, 42]. Frequently care coordinators, social workers, or chaplains can function within a hospital to complete and witness the necessary paperwork for these "informal patient-designated surrogates." Some states require that such forms be notarized or witnessed by non-hospital members.

Also in the absence of a designated decision-maker for an incapacitated patient, medical teams may turn to family members to make decisions for the patient. This is sometimes referred to as "devolved decision-making" [43]. The preferential order will vary by default surrogate statutes in every state; for an excellent overview and interactive map of the varying state procedures for appointing and challenging default surrogates, see DeMartino et al. [44]. The American Bar Association also provides a summary chart of the restrictions placed on default surrogates such as decisions about sterilization, electroshock therapy, or psychosurgery [45].

Recourse to the probate court to appoint a personal or financial decision-maker for an incapacitated patient (i.e., guardian or conservator) is the option of last resort. Petitioning the court is often unwieldly and requires a substantial investment of time and expense [43]. Probate judges may also be called upon to hear emergency cases requiring surrogate decision-makers at the bedside.

Substituted Judgment Criteria

Substituted judgment guidance holds that the surrogate, as an "extension of the patient," should make the decision that would be made by the incapacitated patient if that were possible. Very often in the process of identifying a healthcare representative, a patient may have also created an "advance directive" or "living will," which outlines personal wishes about medical procedures such as life-sustaining care. Though these may provide additional guidance regarding a patient's wishes, these documents are typically informal and, therefore, have limited legal recognition. Clinicians should be aware of applicable statutes before acting on the wishes a patient has outlined in such documents. When there are no explicit instructions, then the surrogate should employ the "best interests standard." From a legal perspective, the best interests standard is considered "objective," though there is no objective means to determine benefits and risks.

Exceptions to Informed Consent

Notwithstanding a history of physicians engaging in treatment and research on human subjects blatantly unethical by today's standards and without the consent or, often, even knowledge on the part of participants, there are four recognized exceptions when a patient's right to make a medical decision can be overridden. These are public health emergencies, medical emergencies, patient waiver, and the rare "therapeutic privilege." Each should be invoked infrequently and with fastidious documentation of the rationale and circumstances.

A public health emergency occurs when the health of a population may depend upon the imposition of certain mandatory measures such as surveillance, testing, isolation, or treatment [46]; the most commonly envisioned scenarios involve either environmental contaminants or infectious contagions. Physicians who would be most impacted would be based in emergency rooms, acute care clinics, intensive care units, and physician's offices. Realistically, individual physicians are unlikely to have control over public health measures and therefore limited ability to negotiate with patients who wish to "opt out" of mandated interventions.

A more likely scenario is a medical emergency, when the provider believes that a delay in medical intervention would result in serious harm to the patient and there is insufficient time to obtain the consent of the patient or their surrogate. Frequently, the patient is unable to give consent because they are brought in unconscious; almost always, the need for informed consent is rendered moot in that situation. Legally, only the emergent condition may be treated without informed consent, and the care should be "directed at goals that, in the opinion of the physician, are in the patient's best interest" [34].

Third, on occasion, an otherwise capable patient may choose to waive their rights and defer decision-making to the physician; in this case the physician is acting as an informal surrogate. This is difficult to show in law and must be "informed, reasoned and voluntary" [47, 48]. In general, there is considerable skepticism about the selective withholding of medical information as medical paternalism has given way to the preeminence of patient autonomy.

Similarly, the doctrine of therapeutic privilege allows physicians to withhold disclosure from patients on the basis that the information would harm the patient. This too has fallen out of favor. With regard to any of the four exceptions, "if any doubt exists as to whether or not to disclose certain information, physicians should always err on the conservative side and disclose" [49, 50].

Special Considerations

Medical Malpractice

Understanding the scope of medical malpractice cases based on flawed informed consent processes is difficult to ascertain as there is tremendous variability in the severity of injuries, the types of surgery, regional standards of care, and patient factors. In one review of spinal surgery malpractice cases, the top specified allegation with regard to informed consent was the failure to explain surgical risks or adverse effects and the failure to explain alternative treatment options [51]. In another, a perceived lack of informed consent was noted as a factor in approximately a quarter of spinal surgery malpractice cases between 2010 and 2015 [52]. In a review of litigated oculoplastic malpractice cases, an alleged lack of informed consent was present in a little less than a third of cases causing authors to emphasize "the importance of a detailed informed consent and clear communication preoperatively regarding patient expectations" [53].

Delegation to Trainees

In an academic environment, surgical teams should bear in mind that the duty to obtain informed consent cannot be delegated [54]. In general, the healthcare provider performing the diagnostic procedure or surgery must obtain the informed consent for the procedure. Studies have indicated that residents who have limited education on informed consent best practices are most frequently asked to complete the task [55]. If trainees are to be involved in the procedures, patients need to be advised of this.

Language Barriers

For patients with limited English proficiency, the use of professional interpreters, rather than family members, to translate may influence the validity of the consent obtained [56]. Family members may have language limitations of their own or have conflicts relating to cultural background or family dynamics [57]. Even with on-site professional interpreter services, hospitalized patients who do not speak English are less likely to have documentation of informed consent for common procedures [56]. If interpreters must be used, their use ought also to be documented in the informed consent note in the record.

Adequate Time for Discussion

This chapter has already discussed allowing sufficient time for patients' questions about the proposed treatment along with their risks and benefits, ideally as part of a longitudinal process. The exigencies of modern surgical practice, with its time constraints and fluctuating schedules, contribute to the difficulties of sustained discussions of material risk. For elective surgeries, the discussion should take place prior to the day of the surgery. For complex, life-changing interventions, such as weight loss surgery, the process of informed consent may extend through multiple meetings between the patient and several members of a multidisciplinary team. For instance, for weight loss surgery, patient education involves meeting with surgeons and discussing the procedure along with meetings with a nutritionist and education about eating patterns expected post-surgery.

Special Populations

The chapters that follow will consider specific operative settings with distinct patient populations, each with unique areas of inquiry with regard to informed consent and capacity. There are two remaining groups of patients whose appropriate management should be considered here.

Jehovah's Witnesses

Jehovah's Witnesses is a Christian denomination with distinct beliefs that differentiate it from mainstream Christianity. Many Jehovah's Witness members do not accept transfusions of whole blood or any blood component [58]. This has given rise to a body of litigation around the right to refuse treatment and Jehovah's Witness patient capacity. In the landmark case *Stamford Hospital* vs. *Nelly E. Vega*, a Connecticut court found in favor of an obstetrical patient who was given blood transfusions against her will though refusal would have led to death [59]. Since the *Stamford* decision over 20 years ago, multiple blood and surgical alternatives can be pursued before transfusions need be considered [58]. However, authors strongly recommend that for Jehovah's Witness operative patients, the informed consent process includes "which transfusion alternatives the patient would accept, who the patient's surrogate decision-maker will be, what information can be discussed with family members, and which decisions should be kept private from family" [60]. Surgical team members should also determine whether a Jehovah's Witness "blood refusal" card is sufficient documentation to serve as a form of advanced directive or whether institution-specific documentation must also be completed.

Emancipated Minors

Whereas a discussion of the informed consent process for minors in general is beyond the scope of this chapter, state laws typically include definitions of "mature or emancipated" minors who may consent for their own care in limited domains. The conditions under which adolescents may make their own decisions vary by state but may be possible with regard to the treatment of sexually infectious diseases, prenatal care, abortion, and substance use. The Guttmacher Institute is an excellent resource for physicians seeking an overview of their state's minors' consent law. Overall, the trend is toward the expansion of areas in which adolescent minors may consent and therefore may be engaged in the informed consent process.

Conclusions

Over the past few decades, traditional medical paternalism has given yield to the modern concepts of patient autonomy and shared decision-making. Physicians have an affirmative obligation to disclose the expected benefits of any proposed treatments as well as their possible harms, invoking exceptions to the informed consent process as infrequently as possible. The rationale for informed consent is predicated on the patient's right to understand what is about to happen to them, and it is a part of the broader commitment to maintaining integrity and trust in the medical profession. This extends far beyond the physician's desire to avoid malpractice, though failures in the informed consent process may be a root cause of preventable litigation.

Rather, the ideal spirit of informed consent is one of mutual understanding between patient and treating physician.

When communicating medical information, physicians would benefit from assessing the amount of information that patients want and are capable of retaining. Physicians may also use a variety of means to enhance communication with the patient and to allow the patient to communicate back to the team. As part of the discussion, it is paramount to discuss the designation of surrogate decision-makers in addition to available treatment options. Consulting psychiatrists not uncommonly have a role to play in assessing capacity, particularly of more vulnerable populations.

Take-Home Points

- Time, patience, and repeated education may well be the most important elements in creating a meaningful informed consent experience for the patient.
- All physicians, not just psychiatrists, ought to assess the decision-making capacity of their patients during every clinical encounter.
- Capacity is decision-specific; rather than concluding that a patient has "global capacity" or assuming that a patient's skill in one domain is applicable elsewhere, treaters must be clear about what the actual "decision at hand" is.
- If the patient lacks the capacity to make a decision, a surrogate decision-maker ought to be identified; even patients without medical decision capacity may be able to understand this choice.

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4 Delirium

Mark A. Oldham

Delirium Defined

Delirium is a neurocognitive disorder of acute confusion due to a general medicosurgical condition or psychoactive substance. Per the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, its two cardinal features are impaired attention and reduced awareness, but beyond these its presentation is heterogeneous [1]. Delirium can present with nearly any neuropsychiatric symptom, and its constellation and severity of symptoms tend to fluctuate over the course of hours and days. As such, accurate recognition of delirium requires deliberate, serial mental status evaluation. Though not a diagnostic criterion for delirium in *DSM-5*, altered arousal is seen in most cases of delirium and should cue clinicians to the potential presence of this condition. Other common features of delirium include anterograde amnesia (i.e., being unable to register new information), thought disorganization, social withdrawal and inanition, sleep-wake cycle disturbances, emotional lability and perceptual disturbances including hallucinations and delusions.

Delirium is common and costly and predicts poor outcomes. Depending on setting, population vulnerability, and severity of medical illness, delirium may occur in upward of 80% of patients and, as such, may be the most common complication after surgery, especially among older adults [2]. The annual cost attributable to delirium among US adults 65 and older alone has been estimated at $164 billion in 2011 US dollars [3], and this is in addition to an incalculable personal toll on patients, their loved ones, and caregivers [4]. As reviewed below, delirium also portends a host of adverse outcomes including accelerated cognitive decline, greater rates of postoperative complications, higher risk of institutionalization, longer hospital and ICU length of stay, and most compellingly higher mortality. Although it may be seen by clinicians as a consternating sequela of medical and surgical care, delirium is a red flag for underlying, often overlooked, illness. Its presence, worsening, or persistence may be viewed as an ancillary vital sign or real-time bioassay that guides clinical decisions [5]. Finally, as with all neurocognitive impairment, delirium can influence a patient's capacity to provide informed consent for treatments and may necessitate identification of a surrogate for medical decisions [6].

The primary goal for delirium management should be prevention where possible. In fact, for two decades, studies have demonstrated that roughly a third of delirium cases may be preventable with non-pharmacological interventions [7, 8]. Although meta-analyses have reached discrepant conclusions on whether

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medications—particularly neuroleptics—prevent delirium, three recent systematic reviews restricted to surgical patients conclude that neuroleptics do prevent postoperative delirium in sufficiently at-risk populations [9–11]. Heterogeneity across studied populations and study interventions continues to confound a clear appreciation of medication's role in preventing delirium (see Management below).

Defining Terms

As described by Lipowski, an early authority in the modern age of delirium research, the word delirium is derived from the Latin *delirare*, meaning to "go out of the furrow," and its earliest use dates to Celsus in the first century A.D. [12]. Acute confusional states have been described for millennia, and descriptions have included variants of psychomotor slowing ("lethargus"), psychomotor activation ("phrenitis"), or mixed presentations. These three behavioral variants of delirium were formally introduced as specifiers in *DSM-5* as hypoactive type, hyperactive type, and mixed level of activity, respectively [1]. One may also specify whether delirium is acute (hours to days) or persistent (weeks to months).

Acute confusional states have garnered scores of terms including toxic-metabolic encephalopathy, acute brain failure, syndrome of cerebral insufficiency, dysergastic reaction, confusional-oneiroid syndrome, ICU psychosis, subacute befuddlement, and, perhaps the clearest to understand, confusion. The term delirium is preferred where its diagnostic criteria are met for the sake of reliability as these other terms lack operationalized diagnostic criteria. Reliability of delirium assessment is necessary for reproducibility of results and real-world generalizability (i.e., external validity).

The term delirium has several, partially overlapping definitions. Broadly, delirium describes a clinical diagnosis as defined by *DSM-5* or, alternatively, by the *International Classification of Diseases, 10th edition* (ICD-10), each of which outlines diagnostic criteria. A diagnosis of delirium describes a *disorder* with a characteristic clinical phenotype and natural history along with the requirement of an associated medical or substance-induced cause. Although neither set of diagnostic criteria include a criterion for time, most studies define delirium by a 24 h day. In contrast, delirium as a *syndrome* describes the characteristic clinical phenotype of delirium including acute-onset disturbance in attention, awareness, and general cognition. Additionally, in clinical parlance, the term delirium is commonly used to describe the neuropsychiatric symptoms of delirium, particularly where they include agitation or combative behavior. For simplicity in this chapter, we will use the term delirium to describe the broader delirium disorder.

Modern delirium literature is spread across specialty journals (e.g., psychiatric, surgical, critical care, geriatrics, hospitalist, palliative care, and nursing), which introduces heterogeneity among reports and often prevents one from making clearly generalizable conclusions about delirium. Delirium in surgical settings, as well, is similarly divided into surgical specialty (e.g., cardiothoracic surgery, gynecologic, orthopedic), surgical candidate (e.g., urgent hip fracture repair vs elective hip replacement), and surgical technique (e.g., laparotomy vs laparoscopy). In this chapter, we will provide an overview of delirium across settings but, where possible, focus on surgical populations.

Clinical Features of Delirium

The core features of delirium may be recalled by the four A's: an *a*cute change in mentation over hours to days characterized by impaired *a*ttention, reduced *a*wareness of one's environment, and at least one *a*dditional cognitive deficit [1] (Table 4.1). We will review each of these in turn. Key to diagnosing delirium is knowledge of a patient's cognitive baseline, which often requires collateral informants who know the patient. The core features of delirium may not be explained fully by pre-existing neurocognitive disorder such as Alzheimer disease.

Impaired attention is defined as a "reduced ability to direct, focus, sustain, [or] shift attention." The term *inattention* is commonly used colloquially though its prefix *in-* suggests "without," yet in

Table 4.1 Common terms used to describe key features of delirium

Term	Definition
Consciousness	This describes one's "state of awareness of self and environment and responsiveness to external stimulation and inner need" [13]. Consciousness has a quantitative aspect (*arousal*) and a qualitative one (*awareness*)
Awareness	Also sometimes referred to as "content of consciousness," [13] this qualitative measure describes the ability to perceive information about one's surroundings and oneself accurately and integrate it into a coherent whole. It ranges from lucidity/"clear sensorium" to confusion/"clouded sensorium" (see Sensorium below)
Attention	This describes the process of selecting an environmental object or mental idea for active processing [14]. Modern neurocognitive models of attention recognize it as multidimensional. Among the facets of attention include alerting to stimulus, focused attention, capacity to shift attention, and sustained attention
Arousal	This is the "level of consciousness," [13] which ranges from *agitation* to *coma*. Arousal is assessed with scales such as the Richmond Agitation-Sedation Scale, Riker Sedation-Agitation Scale, or—toward the lower end of arousal—Glasgow Coma Scale
Agitation	State of significantly heightened psychomotor activity
Alert	State of healthy, waking arousal
Sedation	State of significantly reduced psyc homotor activity
Coma	State of unresponsiveness, without purposeful movements and in which arousal cannot be demonstrated [15]
Sensorium	The integrated whole of sensory experience. In delirium parlance, it qualitatively describes the relative clarity or cloudiness of one's perceptual experience

delirium attention is present but disturbed. A parallel term *dys* attention would be more appropriate. Impaired ability to direct or focus attention or alert to stimulus may be revealed when a patient cannot meaningfully engage in evaluation. That is, a patient may have a glassy-eyed stare or be incoherent. Sustained attention may be assessed by tasks requiring concentration over time such as with reciting the months of the year backward. Impaired ability to shift attention may be revealed when a patient provides the same response to different questions (i.e., perseveration). For instance, a patient may provide the answer "hospital" to the series of questions: "Where are you?", "What year is it?", and "What brought you here?" Common tests for attention are provided in Table 4.2 [16]. Because the symptoms of delirium tend to fluctuate over time, a single assessment for attention may be inadequate to rule out delirium; conversely, the presence of impaired attention has modest specificity for delirium in general [17].

Table 4.2 Common bedside tests of attention (generally in ascending order of difficulty)

Test name	Nature of the test
Vigilance "A" task	Examiner reads a series of letters, and patient indicates when the letter "A" is spoken (e.g., by tapping or by squeezing the examiner's hand)
Forward digit span	Patient repeats number series of increasing length
Reverse digit span	Patient repeats number series of increasing length *in reverse* (e.g., 8-5-2 → 2-5-8)
WORLD in reverse	Patient spells the WORLD in reverse (i.e., D-L-R-O-W)
Days of the week backward	Patient recites the days of week backward
Months of the year backward	Patient recites months of the year backward
Serial 3s	Patient counts backward by 3s from a given number
Serial 7s	Patient counts backward by 7s from a given number (e.g., "Subtract 7 from 100, and keep subtracting 7 until I ask you to stop.")

Disturbance of awareness, more commonly known as confusion, describes the qualitative clarity of a person's thought process. In a broad sense, it answers the question, "Does the patient know what's going on around them?" If a person is grossly disoriented to person, place, time, or situation, one may be reasonably confident that awareness is disturbed. Open-ended questions are key to assessing awareness. A patient's correct responses to a few simple, closed-ended questions such as "Are you in pain?" or "Did you sleep okay last night?" may lead a clinician to conclude erroneously that a patient is thinking clearly. Open-ended variants of these questions "Tell me about your pain" or "How was your sleep last night?" are likely to reveal narrative thought process and, hence, provide a more sensitive measure of awareness.

Diagnosis of delirium requires evidence of an additional disturbance in cognition—that is, beyond disturbed attention and awareness. Common thought disturbances include impaired memory, disorientation, language disturbance, impaired visuospatial ability, or perceptual disturbances. Certain of these may be more obvious than others. A patient who cannot recall that they are in the hospital only minutes after being reoriented represents a prominent deficit, whereas impaired visuospatial ability as evidenced in a patient's inability to draw a clock may require a more sensitive assessment.

Two final diagnostic criteria for delirium are evidence of a secondary cause—be it a medical condition, psychoactive substance, or several concurrent causes (see *Causes of Delirium* below)—and absence of "severely reduced level of arousal, such as coma." Altered arousal is not a diagnostic criterion per *DSM-5* but exists as a diagnostic specifier (i.e., motoric subtypes). Altered arousal is, though, included among the required criteria per ICD-10 [18] and is a core feature of delirium identification per the Confusion Assessment Method. Delirium typically presents with altered arousal [19], which is important because the level of arousal can be assessed within seconds [20]. In fact, the more altered a patient's level of consciousness is, the more likely they are to have delirium, excepting only the extreme ends of the arousal spectrum where patients are incapable of engaging in evaluation (see Fig. 4.1). Regardless of whether one takes an inclusive or restrictive approach to delirium diagnosis vis-à-vis arousal level, serial assessment of arousal with instruments such as the modified Richmond Agitation and Sedation Scale (mRASS) is an efficient means for delirium screening to identify patients who deserve more detailed assessment for delirium.

Figure 4.1 depicts prevalence of mental states and theoretical likelihood of participation in mental status evaluation plotted against level of

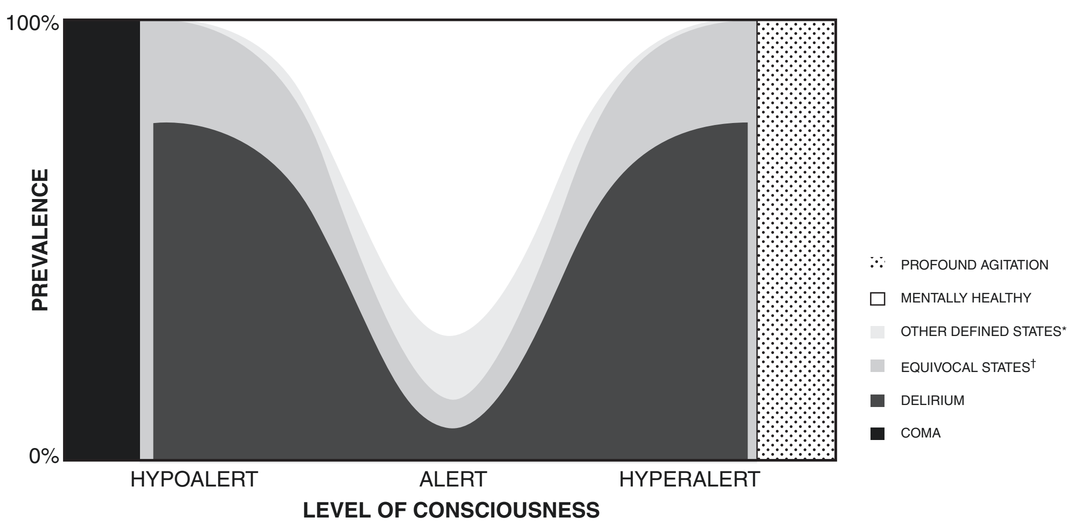

Fig. 4.1 Level of arousal. **Other defined states* include baseline cognitive impairment, primary psychiatric illness (e.g., disorganized psychosis, mania, anergic depression, conversion disorder, dissociation, selective mutism, malingering), catatonia, personality change due to brain injury, sequelae of cerebrovascular accidents (e.g., aphasia, transient global amnesia, locked-in syndrome, abulia, right-brain syndromes), intoxication, sundowning, hypersomnolence as in narcolepsy, or para-ictal states. †*Equivocal states* occur when evaluation is unable to diagnose mental state reliably

consciousness (also called arousal). Prevalence is normalized to 100%. Note that population and setting will determine the relative distribution of mental states as depicted in this figure. For instance, the arousal of marathon runners and residents of long-term care facilities would have dramatically different predictive value regarding mental state.

Sleep and circadian rhythms are universally disrupted in delirium and represent its key non-cognitive feature [21, 22]. Although not included as a diagnostic feature in the *DSM-5*, ICD-10 requires a "disturbance of the sleep-wake cycle, manifested by at least one of the following: (1) insomnia, which in severe cases may involve total sleep loss, with or without daytime drowsiness, or reversal of the sleep-wake cycle, (2) nocturnal worsening of symptoms, and (3) disturbing dreams and nightmares which may continue as hallucinations or illusions after awakening" [18]. Most commonly, patients with delirium have gross fragmentation of sleep-wake cycles with daytime napping and discontinuous sleep at night. In addition, they have significant disruption of endogenous circadian rhythms, which itself may have significant clinical import [23].

Delirium Instruments

The gold standard for delirium diagnosis is generally considered a psychiatric evaluation using *DSM* criteria. Beyond the *DSM*, more than two dozen scales for delirium diagnosis and its severity have been published [24, 25] (Table 4.3). Of these, the Confusion Assessment Method (CAM) is the most commonly used scale by far; as of a decade ago, it had been used for delirium diagnosis in more than 200 studies [26] and has excellent overall performance relative to other delirium screens [27]. A CAM diagnosis of delirium requires (1) acute change in mental status, (2) evidence of impaired attention, and (3) *either* disorganized thoughts *or* altered arousal (i.e., other than alert). Of note, the CAM has been validated for delirium diagnosis for use by trained raters and with the use of a standard cognitive battery. Initially, it was validated for use with the Mini-Mental State Examination but subsequently for use as the short and long form versions and more recently the 3-min diagnostic CAM (3D-CAM) [28]. When used without a formal cognitive screen, its sensitivity may be less than 50% [29]. The CAM and its variations along with training manuals are available at www.hospitalelderlifeprogram.org. They can be used for free clinically and in research with attribution.

The two most common screens for delirium in the intensive care setting are the CAM-ICU and the Intensive Care Delirium Screening Checklist (ICDSC). Although a 2013 meta-analysis found a pooled sensitivity/specificity of 80%/96% and 74%/82%, respectively [30], more recent studies have reported substantially lower sensitivity than early validation studies. For instance, the CAM-ICU was found to have a 50% sensitivity and ICDSC 63% versus the reference-standard diagnosis by *DSM-IV-TR* in an ICU cohort though specificity for both instruments was high at 95% [31]. Further, depending on sensitivity of one's reference standard and population, the CAM-ICU has been found to have as low as 28% sensitivity versus neuropsychiatric evaluation among postsurgical older adults [32]. As described above, clinicians should be aware that the level of arousal also significantly influences psychometric properties of the CAM-ICU and ICDSC [33].

Of the instruments validated for delirium detection in the postanesthesia care unit (PACU), the Nursing Delirium Screening Scale (NuDESC) has been shown to have the highest sensitivity and specificity (95% and 87%, respectively) relative to *DSM-IV* criteria [34], though again the reference standard chosen will influence these properties [32]. Unlike the other instruments described above, which assess a patient's symptoms during a single evaluation, the NuDESC is a nurse-rated scale that is rated toward the end of a nurse's shift after having spent several hours with the patient in routine care [35]. As with all scales, it requires training and clinical expertise.

Several delirium instruments have been developed to assess delirium severity, and among these include the DRS-R-98 [36], CAM-S ("S" for

Table 4.3 Common delirium screening instruments and rating scales

	Time to complete	Number of items	Intended user[a]	Comments
Screening instrument				
Modified Richmond Agitation-Sedation Scale (mRASS)	≤30 s	1	Clinician	mRASS score ≠ 0 is specific for delirium
Intensive Care Delirium Screening Checklist (ICDSC)	≤1 min	8	Clinician	Checklist completed by ICU team after shift
CAM-ICU[b]	≤1 min	9	Clinician	Devised for nonverbal (e.g., intubated) patients
Brief CAM (bCAM)[b]	≤2 min	9	Clinician	Intended for brief assessment (e.g., ED)
3-min Diagnostic CAM (3D-CAM)[b]	3 min	22	Clinician	Efficient, standardized version of the short CAM
Short-Form Confusion Assessment Method (short CAM)[b]	5–10 min	4	Clinician	Primary instrument used in delirium research; must be used with standard cognitive screen
Neelon and Champagne Confusion Scale (NEECHAM)	10 min	9	Nurse	Assesses functional burden of confusion
Nursing Delirium Screening Scale (NuDESC)	≤3 min	5	Nurse	Chosen cutoff (≥ 1 or 2) determines performance
Severity rating scales				
Memorial Delirium Assessment Scale (MDAS)	10–15 min	10	Physician	Incorporates information from collateral sources
Delirium Rating Scale, revised 98 (DRS-98)	Variable	16	Psychiatrist	Provides delirium diagnosis and severity rating
Delirium index	5–10 min	7	Clinician	Must be used with standard cognitive screen
Short CAM-Severity (short CAM-S)[b]	5–10 min	4	Clinician	Short CAM items rated for severity
Long CAM-Severity (long CAM-S)[b]	10–15 min	10	Clinician	Long CAM items rated for severity
3D-CAM-S[b]	3 min	22	Clinician	3D-CAM items rated for severity
CAM-ICU-7[b]	1–2 min	9	Clinician	CAM-ICU items rated for severity

[a]All scales require training for reliable use. Clinician can include a health professional or research assistant trained in clinical use of the scale

[b]Since its introduction in 1990, the CAM has served as a nidus for a range of delirium detection and severity rating scales. Classically, there is a "short CAM," including only the four CAM diagnostic criteria (see text), and a "long CAM," which is the short CAM plus items pertaining to additional features of delirium. These short and long "forms" refer to the operationalized scoring worksheets. These versions of the CAM must be administered in conjunction with a standard cognitive assessment (e.g., mini-cog test, short portable mental status questionnaire, or Mini-Mental State Examination) for reliability. More recent versions of the CAM (e.g., 3D-CAM) have standardized the cognitive assessment to be administered for CAM scoring

severity) [37], Memorial Delirium Assessment Scale (MDAS) [38], and delirium index [39]. As with the delirium detection scales above, these require training for reliability. Such scales are often used to describe the spectrum of delirium symptoms (i.e., phenomenology).

Clinicians who do not deliberately screen for delirium will fail to diagnose a majority of cases [40]. In fact, a review of delirium diagnoses for heart surgery patients (n = 1528) revealed a 12% rate of delirium in the research dataset based on daily delirium assessment but only a 3% rate in the clinical database, suggesting that three quarters of delirium remained undiagnosed in routine clinical care [41]. As one would expect, hypoactive delirium is more likely to be overlooked than its hyperactive counterpart, which is naturally more salient to the casual observer [42].

Unit-wide postsurgical programs to screen proactively for delirium have demonstrated success in reliably detecting delirium and have enhanced the likelihood that such patients will receive delirium-informed care [43]. In fact, a delirium detection program was recently shown to improve length of stay, disposition destination, and patient satisfaction in a cohort of older adults after hip fracture repair [44].

Natural History of Postoperative Delirium

Delirium after surgery is typically divided into four phases: (1) emergence delirium or hypoactive emergence upon awakening from anesthesia, (2) delirium in the recovery room/postanesthesia care unit (PACU) on the day of surgery, (3) delirium on postoperative day 1 (POD 1), and (4) delirium on POD 2 and beyond.

Emergence Delirium or Hypoactive Emergence upon Awakening from Anesthesia

The term emergence delirium is used in anesthesia to describe agitation upon awakening rather than delirium proper. Studies typically describe "inadequate emergence" as encompassing states of elevated arousal (i.e., emergence delirium) and reduced arousal (i.e., hypoactive emergence), though in neither of these subtypes are formal delirium criteria applied. Rates of inadequate emergence range widely due to lack of a consistent definition. The clinical import of agitation during emergence is clear: risk of self-extubation, line removal, or injury to staff or self. Inadequate emergence has also been shown to predict longer stay in the PACU and overall hospital stay [45, 46]. The most consistent risk factor for elevated arousal upon emergence is premedication with benzodiazepine [45, 47, 48]; additional risk factors include higher pain score, longer preoperative fasting time [46], and longer surgery [47]. Younger patients and longer surgery increase risk for reduced arousal upon emergence [45].

Delirium in the Recovery Room/PACU on the Day of Surgery

Few studies have investigated delirium prevalence with the use of formal diagnostic criteria in the hours after awakening in the PACU. In one such study, Sharma et al. identified a 45% rate of delirium among older adults 60 min after isoflurane discontinuation following hip fracture repair [49]. Interestingly, delirium 60 min after awakening from anesthesia had a 100% sensitivity and 85% specificity for subsequent postoperative delirium as assessed daily thereafter. Neufeld et al. independently found the same rate of delirium in the PACU among a mixed surgical cohort of adults over 70 years old, and 74% of all delirium episodes detected during subsequent hospitalization had experienced delirium while in the PACU [50]. Based on limited data, it appears that delirium may be especially common upon awakening from anesthesia, and the hours following emergence may serve as a convenient cognitive stress test for delirium vulnerability and predict subsequent delirium during postoperative course.

Delirium on POD 1

Studies of "postoperative delirium" are divided on whether to begin assessing for delirium on POD 1 or on POD2. This fact introduces heterogeneity into the construct of "postoperative delirium." Questions remain as to whether delirium on POD 1 represents residual effects of anesthesia, postoperative inflammation, or—more likely—some combination of these; additionally, it is unclear whether this distinction matters. Early delirium after surgery, be it either on the day of surgery or POD 1, generally heralds delirium over ensuing days [51]. Moreover, subsyndromal delirium on POD 1 is a risk factor for developing delirium on subsequent days [52]. Roughly three quarters of delirium occurring after surgery will be detected on postoperative days 1 or 2 [53]; conversely, of those who have delirium on POD1, two fifths no longer meet delirium criteria by POD 2 [54].

Delirium on POD 2 and Beyond

Delirium rates tend to peak on POD 2 though a prodrome of cognitive impairment is typically seen prior to delirium diagnosis [55, 56]. This accords well with the known biphasic inflammatory response to tissue injury and, by extension, surgery. Inflammatory mediators peak on POD 2 and subside over the ensuing week [57]. As one would anticipate, a greater severity of delirium on the day of diagnosis predicts higher likelihood that delirium will persist on subsequent days [58]. Although there is great heterogeneity to delirium duration, postoperative delirium typically lasts 2–5 days [59].

Delirium Subtypes

DSM-5 describes three behavioral subtypes of delirium: hypoactive type, hyperactive type, and mixed level of activity. In the postsurgical setting, hypoactive delirium predominates, accounting for two thirds in general postoperative settings [60] to more than 90% in trauma surgery ICU settings [61], in large part due to pharmacological sedation. As noted above, hypoactive delirium is much more commonly overlooked and requires deliberate assessment. Often these patients may be left alone because providers have the impression that they are "just resting," despite the risk of worsening nutrition, persistent immobility, failure to engage in care, etc. In one study, patients with pre-existing dementia were more likely to have hypoactive delirium after hip fracture repair surgery than those without dementia [62]. Inconsistent evidence suggests that hypoactive delirium may be associated with higher 6-month mortality than other subtypes [60].

Hyperactive and mixed level of activity delirium can lead to injury of self, staff, or other caregivers. Mixed level of activity has been linked to inadvertent tube or line self-removals [60]. Patients with predominantly or persistently hyperactive delirium may be monitored closely around the clock for safety, but those with mixed level of activity may be presumed "calm" but become restless or agitated without warning. This unpredictability is likely to explain this elevated risk of unintentional injury. The behavioral subtype of delirium often changes over time even in the same patient [63], a fact which argues further for proactive screening to prevent potentially foreseeable injury.

Subsyndromal Delirium

Delirium is part of a spectrum of neurocognition, and presentations of subsyndromal delirium (SSD) characterized by an insufficient number of delirium features for diagnosis are common. Even when delirium is present, it is commonly preceded by prodromal cognitive impairment [55] as well as followed by residual cognitive dysfunction [64]. SSD is generally thought of as a milder form of delirium that is more common than delirium proper. For instance, SSD has been found in a third of patients after coronary artery bypass grafting (CABG) [65, 66] versus a delirium rate typically ranging from 10% to 20%. SSD and delirium share the same risk factors. Like delirium, SSD deserves prompt management because it often serves as an early warning for impending delirium. In general, outcomes associated with SSD are poorer than matched subjects whose cognition remains intact but more favorable than patients who develop delirium [67].

Delirium Differential Diagnosis

Delirium is a clinical diagnosis defined by diagnostic criteria. Laboratory values, brain imaging, or other studies may elucidate factors that contribute to delirium, fulfilling the diagnostic criterion of evidence for a secondary cause, but they are insufficient in themselves for a diagnosis. Per the *DSM-5*, a diagnosis of delirium precludes all other psychiatric diagnoses while present. This is because delirium can mimic virtually any other psychiatric condition; it can present with anhedonia, depression, mood elevation, anxiety, panic, hallucinations, delusions, paranoia, stereotypies, etc. This exclusion prevents inappropriate diagnosis, for instance, of major depression when a patient's symptoms are rather due to hypoactive delirium or mania in a patient with hyperactive delirium; in fact, roughly 40% of the time when a psychiatrist is consulted in the hospital for depression, the patient's diagnosis is delirium [68–70]. This exclusion also ensures that patients receive adequate workup and management for associated medical and surgical illness (Table 4.4). Diagnosing delirium is a meaningful first step to ensuring that workup is undertaken [71].

Electroencephalography (EEG) has a long history in evaluating delirium and related states of altered mentation, which stretches back to the 1950s and predates the introduction of delirium's operationalized criteria in *DSM-III* (published in 1980) [72]. In their pioneering work, Engel and Romano demonstrated that patients with confusion have diffuse slowing on EEG and that the degree of EEG slowing is correlated with severity of reduced arousal. Modern work in postsurgical and critical care settings has built upon these findings [73]. Relative delta power (i.e., slow waves) on EEG derived from only two electrodes (frontal F8 and parietal Pz) has been shown to discriminate delirium from non-delirium in nonsedated patients after cardiothoracic surgery and thus deserves further refinement and validation [74]. Similarly, bispectral index (BIS), itself derived from EEG using an electrode on each side of the forehead, has similarly been explored as a diagnostic tool for delirium [75]. Whereas BIS has high specificity for delirium (96%) versus CAM-ICU, cortical activity as measured by BIS has a low sensitivity (27%).

Table 4.4 Differential diagnosis for delirium

	Delirium	Dementia	Depression	Schizophrenia	Mania
Timing of onset	Hours to days	Months to years (*note*: vascular dementia commonly has stepwise decline)	Weeks to months	Months	Days to weeks
Age	Risk increases exponentially with age	Risk increases exponentially with age	All ages	Teens to 20s; women more likely to present into 30s; new-onset beyond 50 rare	Bipolar disorder presents in teens to 30s; new-onset beyond 50 rare
Level of arousal	Typically altered; hypo- or hyperactive; may alternate	Normal; evening activation ("sundowning") seen in moderate to severe cases	Normal; may have psychomotor slowing but typically alert	Normal	Hyperactivity; elevated with decreased need for sleep
Key features	Impaired attention and awareness	Indolent decline in cognition, often short-term memory, and overall function (*note*: dementia with Lewy bodies fluctuates)	Dysphoria or anhedonia (i.e., lack of pleasure)	Delusions, hallucinations (typically auditory), and social withdrawal	Euphoria or irritability
Features that suggest an alternative diagnosis	Intact attention, clarity of thought, no evidence of secondary cause	Acute-onset, symptom fluctuation, altered level of arousal	Acute-onset, altered level of arousal, impaired attention or awareness; gross confusion	Acute-onset, late-onset, altered level of arousal, impaired attention/ awareness, non-auditory hallucinations	Late-onset, fluctuating symptoms, impaired attention/ awareness

Neurobiology of Delirium

Extensive reviews on the neurobiology of delirium have been published [76, 77]; however, the complexity of delirium and its biological determinants have stymied a succinct model of the condition. As outlined by Maldonado, at least seven biological delirium models have been propounded. These include neuroinflammation, oxidative stress, neuronal aging, neuroendocrine abnormalities, sleep and circadian rhythm disturbance, network dysconnectivity, and neurotransmitter dysregulation. Although these seven models interact substantially, it remains to be proven the degree to which current delirium models represent either (a) different levels of concurrent or serial processes (e.g., advanced age leading to subcortical, small vessel disease, reducing network resilience, and finally presenting as neurotransmitter dysregulation and delirium); (b) independent, biologically coherent diseases with convergent phenotype (e.g., oxidative stress after stroke, network dysconnectivity in postictal encephalopathy, neurotransmitter [glutamate] dysregulation in NMDA receptor antibody encephalitis); or (c) some combination of the two.

Surgery provides a reliable clinical paradigm for investigating delirium neurobiology and vulnerability because surgical cohorts are exposed to similar physiological insults, and the natural course of delirium can be observed in the perioperative period. The neuroinflammatory model of delirium has received the greatest attention in postoperative delirium studies. Patients with delirium tend to have a higher ratio of proinflammatory to anti-inflammatory chemokines than those who remain non-delirious [78], and early elevations the day of surgery may predict delirium over subsequent postoperative days [79, 80]. Interleukin-6 (IL-6) and interleukin-8 (IL-8) each appear to have a unique temporal association with delirium after surgery. Low CSF IL-6 prior to surgery is a risk factor for delirium [81], and elevations in serum IL-6 are observed *during* delirium [82–84], with the highest values in patients with hyperactive delirium or delirium with mixed level of activity [84]. However, elevations in IL-8 may be seen *before* delirium presentation [84, 85]. IL-1β, IL-2, and TNF-α have also been implicated in postoperative delirium but remain less studied [86, 87].

Investigations of the hypothalamic-pituitary-adrenal (HPA) axis in the perioperative setting have also revealed insights into the neurobiology of delirium. For instance, elevated cortisol before CABG has been found in association with post-CABG delirium [88]. Both absolute cortisol values on POD1 and relative change in cortisol relative to preoperative values have been found associated with delirium as well [89]. Similar to IL-8, cortisol elevation may be seen prior to delirium onset [85]. Interestingly, the interaction between degree of inflammation and cortisol response also appears to play a role in elevating risk of delirium [89].

Though sleep and circadian rhythm disruption have been described in delirium from time immemorial, such disruption may offer further insights into the neurobiology of delirium. In fact, Lipowski suggested conceptualizing delirium as a "disorder of wakefulness" as a way to build upon our understanding of delirium physiology [12]. As reviewed recently, delirium is associated with broad disruption in endogenous circadian rhythms and sleep-wake cycles and often involves chaotic endogenous circadian rhythms with fragmentation of sleep and wake over the 24 h cycle [23]. Sleep disruption is nearly universal in delirium and may also confer vulnerability to delirium [90].

Several other lines of investigation exploring the biology of delirium remain active. Notable areas of inquiry include polymorphisms in genes encoding for glucocorticoid, glutamate or dopamine receptors [91–93], S100B elevations in serum or CSF indicative of neuronal injury [94], and studies of neurotransmitter precursors (e.g., serotonin [95]) or their metabolites (e.g., norepinephrine [96]). The role of serum anticholinergic activity in delirium remains unsettled. Although early studies found elevated anticholinergic activity in POD [97, 98], modern studies have revealed that these differences may be confounded by failure to account for preoperative values [99] or for cognitive status and degree of inflammation [100].

Outcomes After Delirium

Most studies investigating outcomes after delirium find delirium to be an independent risk factor for several cognitive and functional sequelae; however, the heterogeneity across studies (e.g., study population, method of delirium diagnosis, postoperative days on which delirium is assessed) introduces variance in findings. In addition, studies vary widely in adjusting for covariates, and this influences outcomes [101].

Delirium after hip fracture repair may prolong hospitalization by a week and is associated with substantially increased cost per patient [102], reduced likelihood of return to pre-fracture level of ambulation, and elevated risk of decline in basic activities of daily living at 1 year [103]. In a longitudinal study, researchers found that 2 years after hip fracture surgery, fewer than half of patients who developed postoperative delirium survived versus two thirds of those without delirium, and among survivors nearly four in five of those who had developed postoperative delirium a year earlier had mild cognitive impairment or dementia relative to the 40% in those without delirium history [104]. Three years after hip fracture surgery, delirium has been associated with cognitive impairment (OR 41.2) including subjective memory decline (OR 6.2) and incident need for long-term care (OR 5.6) [105]. Not only does delirium predict mortality in general, each day delirium is associated with an increased hazard of dying over 6 months postoperatively by 17% [106].

Outcomes after other types of surgery have also been explored [107]. Delirium after heart surgery is associated with functional [108] and cognitive [109] impairment 1 month after cardiotomy, but these effects were no longer seen at 1 year. Patients with post-CABG delirium based on chart review (i.e., without assessment by research personnel) were found to have a greater all-cause mortality 5 years after surgery (86% vs 80%) based on national registry data [110], and 1-year follow-up by questionnaire after cardiotomy indicated that patients with postoperative delirium had a significantly higher mortality (13%) than those without (5%) along with a higher rate of hospital readmission over the first postoperative year [111]. Long-term outcomes after postcardiotomy delirium may not be as dire as those after hip fracture repair, in part owing to the greater frailty of patients who develop hip fractures.

A range of poor outcomes associated with delirium have been identified in mixed surgical and other specific surgical cohorts. Meta-analysis has revealed that after critical illness, itself not limited to surgical patients, delirium is associated with higher in-hospital mortality (RR 2.2), longer duration of mechanical ventilation (SMD 1.8), and prolonged ICU length of stay (SMD 1.4) [112]. Three separate mixed surgical cohorts ((1) older adults undergoing major orthopedic, vascular, or abdominal operations, (2) abdominal aortic aneurysm repair and colorectal cancer surgery, and (3) major abdominal, thoracic, or vascular surgery) have independently identified increased length of stay, higher readmission rates, and greater risk of institutional discharge associated with postoperative delirium [59, 113, 114]. Delirium after orthotopic liver transplant predicts longer hospitalization, a fourfold risk of dying in-hospital, and a threefold risk of 1-year mortality relative to non-delirious referents [115]. Finally, delirium after resection for esophageal cancer is associated with longer stay in the hospital and specifically in the ICU [116].

Causes of Delirium

Delirium is due to a biological insult that exceeds an individual's neurophysiological resilience (or "cognitive reserve"). As such, it involves the interplay of (1) underlying neurophysiological integrity; (2) integral pro-cognitive factors such as nutritional status, intact sleep and circadian rhythms, and adequate cognitive stimulation; and (3) external biological insults. Clinically, these three may be considered as some combination of predisposing or precipitating factors [117]. One may also consider underlying neurophysiological vulnerability and disruptions in pro-cognitive factors as perpetuating factors of delirium as well. A vast list of contributors to postsurgical delirium have been studied extensively in the literature. Here we limit the discussion to the most consistently identified factors thought to predispose, to precipitate, or to perpetuate delirium.

Predisposing (Risk) Factors for Delirium

Identifying risk factors is critical for risk stratification so at-risk populations are screened proactively for delirium so that targeted intervention can be initiated. More than a hundred risk factors for delirium have been identified across clinical settings. Universal risk factors for delirium include advanced age, cognitive impairment, and functional limitations including severity, acuity, and complexity of medical illness as well as general frailty [118, 119]. Broadly, delirium risk factors may be considered potentially modifiable or non-modifiable or, alternatively, categorized temporally relative to surgery itself—preoperative, intraoperative, or postoperative. Although risk factors for delirium are often consistent across settings, certain variables do vary based on surgical population. That is, each surgical intervention serves a population with shared clinical features and vulnerability types, so each surgical population (e.g., patients undergoing hip fracture repair surgery) may have a signature pattern of delirium risk factors that reliably differs from other populations. Here we consider risk factors based on surgical intervention (Table 4.5).

Based on meta-analysis (24 studies, pooled $n = 5364$), the best described delirium risk factors after hip fracture repair include cognitive impairment, advanced age, institutional residence, heart failure, total hip arthroplasty, multimorbidity, morphine use, and male gender [120]. The type of orthopedic surgery also influences cohort and associated delirium risk. Significantly, hip fracture repair is associated with nearly twice the risk of delirium as elective arthroplasty, an effect seen among both cognitively intact and cognitively impaired subjects [121]. In addition, patients presenting for surgical repair of hip fracture are more likely to have preoperative delirium than elective surgical candidates. Common preoperative delirium predictors after spinal surgery include advanced age, polypharmacy, female gender, and low hematocrit or albumin (6 studies, pooled $n = 580{,}902$ [*note*: one study included a nationwide sample]) [122].

After heart surgery (25 studies, pooled $n = 5121$), consistent predisposing factors include age, cognitive impairment, depression, stroke history, diabetes mellitus, and atrial fibrillation [123]. It is notable that these final three factors reflect risk of cerebrovascular disease and brain ischemia. Rudolph et al. have further demonstrated carotid artery stenosis is associated with risk of post-CABG delirium [124]. Systematic review of delirium risk factors after vascular surgery has similarly been undertaken (10 studies, pooled $n = 1892$) [125]. Beyond advanced age and cognitive impairment, additional delirium predictors after vascular surgery include multimorbidity, depression, tobacco use, and open (vs endovascular) repair.

Table 4.5 Delirium risk factors by surgical cohort

Universal risk factors	Hip fracture cohorts	Spine surgery cohorts	Heart surgery cohorts	Vascular surgery cohorts	GI surgery cohorts	Critical care cohorts
Advanced age Cognitive impairment Functional impairment Severity, acuity, and complexity of medical illness Overall frailty	Male gender Institutional residence Heart failure Total hip arthroplasty Morphine use	Female gender Polypharmacy Low hematocrit Low hemoglobin	Stroke history Depression Diabetes mellitus Atrial fibrillation	Depression Tobacco use Open vascular repair	Low albumin Physical (ASA) status Alcohol abuse history Higher body mass index	Hypertension Pre-ICU emergent surgery APACHE II score Mechanical ventilation Metabolic acidosis

Two other notable populations include GI surgery and subjects in the surgical ICU. Based on 11 studies (pooled $n = 1427$), advanced age, low albumin, physical status per American Society of Anesthesiologists, alcohol abuse history, and body mass index predict delirium after GI surgery [126]. Meta-analysis of delirium risk factors among mixed medical/surgical critically ill populations has identified the following: age, dementia, hypertension, pre-ICU emergent surgery, acute physiology and chronic health evaluation (APACHE) II score, mechanical ventilation, and metabolic acidosis [127].

Beyond individual risk factors, roughly two dozen postoperative delirium risk prediction models have been published, though most have not been adequately validated or studied independently for reproducibility [128]. For instance, Jansen et al. applied eight such instruments in an independent population of elective surgery patients; the highest area under receiver operating characteristic curve was 0.66, suggesting overall poor predictive value [129]. The authors acknowledge that the prediction models were not applied precisely as originally studied (e.g., population differences and separate delirium assessment tool), but these results reveal how delirium risk may be unique to population, setting, shared vulnerabilities, and perhaps also delirium detection strategy.

Several intraoperative risk factors have been identified, but anesthesia type (i.e., general vs regional) has yet to be conclusively identified as one of these. A review of 21 studies (pooled $n = 2108$) found that anesthesia type was not statistically associated with postoperative delirium though general anesthesia exhibited a nonsignificant associational trend with cognitive dysfunction after surgery [130]. Consistent evidence implicates surgery duration, intraoperative hypotension, requirement of blood transfusion, and invasiveness of surgery in raising postoperative delirium risk. Several postoperative "risk factors" for delirium include prolonged intubation, elevated inflammatory markers, fever, electrolyte abnormalities (e.g., hyponatremia), and postoperative complications, though several of these are more appropriately delirium precipitants or proxy measures thereof than predisposing factors.

Delirium Precipitants

If a patient's clinical presentation meets criteria for delirium, then its underlying precipitant(s) should be sought. Two or more causes will be found in more than half of cases of delirium. The list of potential precipitants is extensive, so mnemonics are commonly used to aid in their recall. Two common acronyms include WWHHHHIMPS and I WATCH DEATH [131]. The first of these catalogs delirium causes that are life-threatening or whose failure to diagnose can lead to irreversible sequelae. These are *W*ernicke encephalopathy, *w*ithdrawal, *h*ypertensive crisis, *h*ypoperfusion of the brain, *h*ypoglycemia, *h*yper-/*h*ypothermia, *i*ntracranial process/*i*nfection, *m*etabolic/*m*eningitis, *p*oisons, and *s*tatus epilepticus. The second of these acronyms, which bespeaks of delirium's elevated risk of mortality, provides a categorical approach to identifying delirium cause(s) (Table 4.6). One final mnemonic is END ACUTE BRAIN FAILURE, which incorporates both predisposing and precipitating factors [132]. It stands for *e*lectrolyte imbalance and dehydration, *n*eurological disorder and injury, *d*eficiencies, (advancing) *a*ge, *c*ognitive impairment, *u*rine toxicology (intoxication and withdrawal), *t*rauma, *e*ndocrine disturbance, *b*ehavioral (i.e., depression or schizophrenia as a delirium risk factor), *R*x and other toxins, *a*nemia/anoxia/hypoxia/low perfusion states, *i*nfections, *n*oxious stimuli (i.e., severe pain), *f*ailure (organ), *A*PACHE score (illness severity), *i*ntracranial process, *l*ight/sleep/circadian rhythm, *u*remia/other metabolic disorders, *r*estraints/immobility, and *e*mergence delirium.

Delirium Perpetuation

Every additional day of delirium in the hospital predicts greater risk of subsequent morbidity and mortality [106, 135], and persistent delirium 6 months after index hip fracture surgery is associated with nearly three times the 1-year mortality of those without such persistent delirium [136]. As opposed to robust evidence for predisposing and precipitating factors for delirium, factors

Table 4.6 Delirium precipitants

Inflammation	Infection: urinary tract infection, pneumonia, sepsis, brain/epidural abscess, osteomyelitis, endocarditis, meningitis, encephalitis, and *many more* Post-infectious: acute disseminated encephalomyelitis, antibody-associated encephalitis Autoimmune: antibody-associated encephalitis or rheumatic conditions associated with cerebral involvement (e.g., neurolupus) [133]
Withdrawal	Alcohol Sedative-hypnotics: benzodiazepines, barbiturates
Acute metabolic disturbance	Organ failure/decompensation: liver failure/hepatic encephalopathy, uremia Electrolyte abnormalities: ↑/↓ sodium, ↑ calcium, ↓ phosphate, ↑/↓ serum pH Inborn errors of metabolism [134]
Toxins	Medication (toxicity/intoxication): lithium, valproate, benzodiazepines, opioids, tacrolimus, and *many more* Medication (side effect): valproate-induced hyperammonemia, neuroleptic malignant syndrome, serotonin syndrome Drugs of abuse: alcohol, opioids, designer drugs, stimulants Over-the-counter medications: anticholinergics Floral: Jimson weed, oleander, foxglove, hemlock, belladonna Heavy metals: mercury, copper, lead, manganese Others: insecticides/pesticides, solvents, poisons, ethylene or propylene glycol
CNS	Seizure-related Space-occupying: tumor, gliomatosis/lymphomatosis/carcinomatosis cerebri Normal pressure hydrocephalus Neurodegenerative: alpha-synucleinopathy Demyelinating disease: osmotic demyelination syndrome, ADEM (as post-infectious above), delayed post-hypoxic leukoencephalopathy Other: Marchiafava-Bignami syndrome, mitochondrial encephalopathy, progressive multifocal leukoencephalopathy, prion disease, complex migraine
Hypoxia	Severe anemia, carbon monoxide or cyanide poisoning, methemoglobinemia, respiratory failure, low atmospheric oxygen
Deficiency	Thiamine, niacin, pyridoxine, cyanocobalamin
Endocrine	↑/↓ glucose, ↑/↓ thyroid status, adrenal insufficiency, hypercortisolemia
Acute vascular	Perfusion-related: stroke, myocardial infarction, blood loss, increased intracerebral pressure, coagulopathy, fat/septic embolism Hemorrhage-related: subarachnoid hemorrhage, subdural/epidural hematoma, intraparenchymal hemorrhage Hypertensive encephalopathy with or without posterior reversible encephalopathy syndrome
Trauma	Postoperative state (inflammatory) Blunt-force: traumatic brain injury, diffuse axonal injury Electrocution Thermal: burns, heat stroke, hyperpyrexia, hypothermia
Hematologic	Thrombotic thrombocytopenia, diffuse intravascular coagulation, hemolytic uremic syndrome, thrombocytosis, hyperviscosity syndrome, blast cell crisis, tumor lysis syndrome

that perpetuate delirium have received nominal attention. Further, given that delirium can persist or inaugurate long-term cognitive impairment [137–139], identification of perpetuating factors should be sought. Keys to recovery include adequate oxygenation, hydration, nutrition, adequate sensory stimulation, mobility, maintained sleep-wake cycles, cognitive activation, and socialization.

Clinical Management of Delirium

Several clinical guidelines on delirium management have been published, each of which emphasizes a specific setting and population. As pertains to delirium in hospitalized patients, the American Geriatrics Society (AGS) describes best practices for managing postoperative delirium in older adults [140]. The American College of Critical

Care Medicine provides guidelines for the management of pain, agitation, and delirium (PAD) in critically ill adults [141]. The European Society of Anaesthesiology has published evidence- and consensus-based guidelines on managing postoperative delirium [142]. Lastly, the UK National Institute for Health and Clinical Excellence (NICE) has also offered clinical guidelines, which address the broader aims of delirium diagnosis, prevention, and management [143]. Whereas guidance is broadly aligned across these guidelines, it should be kept in mind that the different settings and guideline methodologies contribute to distinctions on specific clinical recommendations.

Proactive Delirium Identification

Delirium is commonly overlooked during routine care without proactive screening. Early identification is imperative for prompt identification of underlying causes, particularly in frail older patients. In fact, delaying even symptomatic treatment of common features associated with delirium (e.g., autonomic activity, psychosis, anxiety) may lead to worse clinical outcomes [144]. There is a consensus among guidelines that at-risk patients should be monitored for delirium at least daily—if not every nursing shift—starting the day of admission using a validated instrument (e.g., CAM-ICU or ICSDC in the ICU, NuDESC in the recovery room and postoperative setting, CAM on general medicine). Such screening and care coordination is best delivered by a multidisciplinary team that delivers personalized care [140].

Delirium Prevention

Best management for delirium is prevention where possible, and up to 40% of delirium may be preventable depending on population [140]. Non-pharmacological interventions are recommended for delirium prevention in patients at elevated risk, particularly older adults with cognitive and functional impairment [8]. Typically, more than one intervention is implemented at the same time, creating so-called delirium bundles. The two best-studied delirium bundles are the Hospital Elder Life Program (HELP) for hospitalized older adults [145] and the ABCDEF bundle designed for critical care [146]. Such care bundles involve nursing and rehabilitative care that facilitates orientation to environment, sensory support including visual and hearing aids as needed, cognitive stimulation, and proactive mobility, especially early ambulation after surgery. Other key factors include ensuring adequate hydration, nutrition, oxygenation, as well as assertive pain control that minimizes opioids where feasible. Healthy sleep patterns and sleep hygiene are critical to recovery [23]. This should include clustered care overnight to limit number of awakenings and minimizing noise and light pollution that may disrupt sleep. Catheters and lines should be reviewed regularly for clinical indication to prevent infection and medications reviewed for agents that may contribute to delirium including those with anticholinergic activity, benzodiazepines, and opioids. Proactive geriatrics consultation may also be considered for delirium risk stratification and to address potentially modifiable risk factors [147].

Pharmacological prevention of delirium remains controversial. Although data support the efficacy of neuroleptics to prevent delirium in sufficiently at-risk populations, their potential for side effects make them ill-suited for routine use. A recent review found that three of the four randomized, placebo-controlled trials investigating neuroleptics for the prevention of postoperative delirium yielded positive results [148]. There was only one study where neuroleptic failed to prevent postoperative delirium relative to placebo (15% vs 16%, respectively); however, this same study found that haloperidol nevertheless statistically reduced delirium severity (highest DRS-R-98 score 14 vs 18), delirium duration (5 vs 12 days), and hospital stay (mean difference 5.5 days) [149]. Two separate meta-analyses have found that neuroleptics may reduce the risk of postoperative delirium by nearly a half in sufficiently at-risk older surgical populations [11, 150], and two additional systematic reviews concluded that neuroleptics prevent delirium though refrained from meta-analysis given substantial heterogeneity across studies [9, 10].

Dexmedetomidine infusion is associated with lower risk of delirium relative to propofol sedation [151] or analgosedation with opioids [152]; however, consensus has yet to emerge over whether it reduces delirium relative to placebo as conflicting reports exist [153–155]. Based on current evidence, cholinesterase inhibitors (e.g., donepezil or rivastigmine) should not be used to prevent delirium. Not only have these agents failed to prevent delirium in randomized, placebo-controlled trials [148], but a multicenter randomized trial of assertively titrated rivastigmine for delirium prevention was discontinued early as the mortality in study patients was nearly three times as high as the placebo group (22% vs 8%, respectively) [156].

Melatonergic agents have been studied for their potential to prevent delirium though studies on their efficacy in managing delirium are lacking [23]. Although early small studies of evening melatonin to prevent delirium were positive [157–159], the largest and most rigorous study to date was unable to find that melatonin alone reduced risk of delirium, though melatonin was associated with delirium of shorter duration [160]. This could suggest that healthy circadian rhythms prevent delirium perpetuation. Clinicians should keep in mind that melatonin is a chronobiotic agent that modulates circadian rhythms, not a sleep aid. Therefore, it ought to be administered several hours before bedtime, before the onset of endogenous dim light melatonin onset, to stabilize circadian rhythm. One further, randomized-controlled trial found that the melatonin agonist ramelteon led to a marked reduction in new-onset delirium among older adult inpatients relative to placebo (3% vs 32%) [161]. Several studies exploring the potential for circadian interventions to prevent delirium are underway.

A parallel body of literature has investigated the role of lighting on delirium prevention and management. Early small studies of morning light therapy in surgical cohorts reported positive results in reducing delirium [162, 163]; however, a recent large-scale study found that ICU patients randomized to blue-enhanced light condition did not have a lower risk of delirium relative to standard lighting [164], suggesting that at least in ICU timed bright light as a single intervention may be insufficient for preventing delirium.

Finally, several surgical and anesthetic variables are relevant to delirium prevention. Fast-track surgery, also known as enhanced recovery after surgery, is recommended as standard of care [142]. This involves several elements of peri- and postoperative care designed to expedite postoperative recovery and reduce hospital length of stay [165]. In general, less-invasive procedures are associated with lower rate of postoperative delirium. For instance, endovascular aortic aneurysm repair is associated with less than half the delirium risk of open repair (13% vs 29%, respectively) [166]. Depth of anesthesia should be monitored carefully because BIS-guided depth of anesthesia has been shown to reduce risk of postoperative delirium [167–170]; however, no clear guidance is provided on how best to titrate anesthesia depth given the risk for surgical recall upon awakening with light anesthesia. In general, benzodiazepine premedication prior to anesthesia should be reserved for patients with severe anxiety. Some authors have also indicated that continuous intraoperative analgesia as with remifentanil may be recommended to bolus administration [142].

Delirium Management

Once delirium is identified, the initial steps are to establish a differential diagnosis, treat any underlying cause(s), and address other potential contributors such as nutritional status, hydration, etc. In this way, treatment targets the neurophysiological disturbances of delirium. However, treating delirium also often involves management of its neuropsychiatric features. Although it remains to be seen whether multicomponent, non-pharmacological bundles shorten or reduce the severity of delirium, these should be instituted broadly to ensure that sensory deprivation, sleep fragmentation, malnutrition, dehydration, and immobility do not perpetuate delirium.

Hypoactive delirium is best managed non-pharmacologically. Such patients typically require assertive nursing care for daytime activation, ensuring that they are out of bed each day. In these patients, physical and occupational therapy may assist with regular ambulation, and patients should be provided with cognitive stimulation. For instance, the "delirium toolbox" is one such innovative approach to addressing sensory impairment, stimulating cognition, and promoting health sleep [171]. No medication is currently approved by the US Food and Drug Administration for the prevention or management of delirium. Although stimulants and non-stimulant wake-promoting agents (e.g., modafinil) have been used anecdotally to address daytime torpor in hypoactive delirium, their use in this population has not been studied in clinical trials. In addition, stimulants increase the risk of psychosis and perhaps transitioning a patient from hypoactive to hyperactive or mixed level of activity delirium.

Hyperactive delirium deserves dedicated nursing care for comfort and safety. First-line management should involve verbal and nonverbal de-escalation, including redirection where possible. Though physical restraint may be unavoidable in certain cases, restraint-free units have been developed and championed for older adults with delirium. Such rooms focus on non-pharmacological approaches from trained staff. One example of this model is the Delirium Room, which abides by the core principles of "tolerate, anticipate, and don't agitate" (or T-A-DA method) [172]. That is, tolerate certain non-threatening behaviors reasonably attributable to delirium; anticipate the potential for unintentional, impulsive behaviors or need for frequent redirection; and do not introduce further stimulation where a patient is already activated or may be at risk of overstimulation.

Despite the common use of neuroleptics for the management of hyperactive delirium or delirium with mixed level of activity, large randomized, placebo-controlled efficacy trials are lacking. Although recent reviews have been unable to identify compelling, placebo-controlled evidence to support the use of neuroleptics in delirium [173, 174], scores of studies have been conducted that compare neuroleptics against one another or against benzodiazepines. Clinicians are well-aware of the calming effects that neuroleptics can have on restless, agitated, or combative patients, and the possibility of randomizing a patient to receive placebo for acute behavioral crises is a daunting prospect. More than 30 studies of neuroleptics for delirium have been conducted to date, most of which have been either open-label or used active controls such as another neuroleptic or benzodiazepine [132].

Based on one randomized clinical trial, the PAD guidelines find evidence that atypicals (viz., quetiapine) may reduce delirium duration relative to placebo [141], whereas the NICE guidelines recommend consideration of haloperidol or olanzapine for short-term management of delirium, starting with the lowest clinically appropriate dose [143]. All guidelines agree with avoiding the use of benzodiazepines in delirium except when due to alcohol or benzodiazepine withdrawal where benzodiazepines are first line [175]. The words of caution expressed in the AGS guideline deserve attention, namely, that antipsychotics at the "lowest effective dose for the shortest possible duration may be considered to treat delirious patients who are severely agitated or distressed or who are threatening substantial harm to self/others" [140]. See Table 4.7 for neuroleptics commonly used in delirium.

Summary

Delirium is a common, costly, and disabling state of confusion due to the interaction between biological insults and physiological vulnerability. Its cardinal features include an acute change in attention and awareness plus at least one additional cognitive deficit. Sleep-wake cycle disturbances are ubiquitous in delirium, and most patients present with altered, often fluctuating,

Table 4.7 Neuroleptics commonly used for management of delirium symptoms[a]

Neuroleptic	Formulations	Starting dose	Maximum daily dose	QTc change[b]	Notable features
Haloperidol	PO, IM, IV[c]	1–2 mg	20 mg	4.7 ms	Risk for extrapyramidal symptoms (EPS) IV route with less EPS but greater effect on cardiac conduction No anticholinergic activity PO bioavailability roughly 60% ~24 h half-life
Risperidone	PO, ODT, oral liquid	0.5–1 mg	6 mg	11.6 ms	Risk for EPS ODT or liquid may prevent pill cheeking or spitting ~24 h half-life
Quetiapine	PO	25–50 mg	200 mg[d]	14.5 mg	Very limited risk of EPS Moderate QTc prolongation Sedating (antihistaminic) Causes orthostatic hypotension (α_1 antagonist) 6 h half-life
Olanzapine	PO, ODT, IM[e]	2.5–5 mg	20 mg	6.8 mg	Limited risk of EPS Mild QTc prolongation Sedating 30 h half-life
Aripiprazole	PO, ODT, IM	2–5 mg	30 mg	Limited	Akathisia in a third of patients Limited, if any, effect on QTc 72 h half-life

Abbreviations: *IM* immediate acting intramuscular, *IV* intravenous bolus, *ODT* orally disintegrating tablet, *PO*, oral
[a]All agents are off-label for management of delirium, and neuroleptics carry a black box warning for "increased mortality in elderly patients with dementia-related psychosis"
[b]https://www.fda.gov/ohrms/dockets/ac/00/backgrd/3619b1b.pdf
[c]Many hospitals compound this though haloperidol is not indicated for intravenous administration in the USA
[d]Quetiapine is seldom used over 200 mg a day in managing neuropsychiatric features of delirium though, depending on its psychiatric indication, may be used up to 800 mg a day after cautious titration over weeks
[e]IM olanzapine should not be used with benzodiazepines as this combination risks fatal respiratory suppression

level of arousal. Critically, although acute symptoms commonly resolve, an episode of delirium can inaugurate long-term cognitive and functional decline and predicts a range of poor outcomes. Accurate delirium detection requires proactive screening, which can be done expediently with a variety of valid instruments such as the CAM, CAM-ICU, and NuDESC. Assessing for level of arousal has been proposed as an efficient means of delirium screening. Wherever possible, delirium prevention is key. Best treatment involves reversing delirium precipitants; shoring up pro-cognitive factors such as nutrition, hydration, mobility, and cognitive activation; and addressing its neuropsychiatric features where necessary. Hypoactive delirium is typically best managed without recourse to psychopharmacological agents, though judicious use of neuroleptics may be considered for severe, distressing, or dangerous symptoms of hyperactive delirium.

Take-Home Points

1. Paralleling the course of post-injury inflammation, postoperative delirium peaks on postoperative day 2 and lasts 2–5 days.
2. Universal risk factors for postoperative delirium include advanced age, cognitive and functional impairment, multimorbidity, and greater invasiveness of surgical procedure.
3. Most cases of delirium—especially hypoactive delirium—will be overlooked without routine use of delirium screening instruments.

4. Non-pharmacological interventions can prevent up to a third of delirium in at-risk populations.
5. Whereas non-pharmacological interventions should be first line for managing behavioral features of delirium, judicious use of neuroleptics may be considered for severe, distressing, or dangerous symptoms.

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5 Management of Psychiatric Medications During Perianesthesia Period

Paula Trigo-Blanco and Adriana Dana Oprea

Introduction

Up to 10% of the population has a psychiatric illness. The World Health Organization (WHO) reported in 2001 that about 450 million people worldwide suffer from some form of mental disorder or brain condition and that one in four people meet sufficient criteria to be diagnosed at some point in their life [1]. With such high prevalence in the community, these conditions are commonly found in patients undergoing surgery and anesthesia. Moreover, it is likely that these patients have other comorbidities (e.g., cardiovascular disease), which may increase the risk of perioperative adverse events, in addition to potential interactions between anesthetics and their psychotropic medications. Therefore, these patients deserve close monitoring during the perioperative period, especially when their medications may interact with the effects of anesthetic drugs [2, 3].

Developing a patient-specific anesthetic plan for surgery includes preoperative evaluation of individual risk, optimization of comorbidities before surgery, and a general preference for short-acting agents for induction and maintenance of general anesthesia. Specifically, potential interactions between psychotropic drugs and anesthetic agents should be considered during preoperative evaluation. In this chapter, we describe each class of psychotropic medications, their proposed mechanisms of action, and their potential side effects, with a focus on potential interactions with medications used in the perioperative period. The most common drugs used by the anesthesiologist and their interactions with psychotropic medications are summarized in Table 5.1.

Psychotropic Medications by Class and Implications for Anesthesia

Antidepressants

Major depression is one of the most common mental disorders worldwide, and antidepressants are the most commonly prescribed class of medication in the USA. Antidepressants are commonly divided into four groups: selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors (SSRIs/SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and atypical agents (see Table 5.2).

Given the relative safety of antidepressants with anesthetics as well as the risk of a discontinuation syndrome and loss of antidepressant effect upon cessation, it is generally

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Table 5.1 Anesthetics and their implications for psychopharmacologic treatment

Class of anesthetics	Medications	Mechanism of action	Dose	Route of administration	Interaction with psychotropic medications	Comments
Intravenous anesthetics	Barbiturates *Thiopental* *Methohexital*	GABA activation	3–5 mg/kg 1–1.5 mg/kg	Intravenous, intrarectal, intramuscular	Tricyclic antidepressants (TCA)—increased toxicity, seizures	*All intravenous anesthetics potentiate CNS depression associated with psychotropic medications*
	Propofol	GABA activation	1–2.5 mg/kg (induction) 25–250 mg/kg/min (maintenance)	Intravenous	Not described	
	Etomidate	GABA activation	0.2–0.3 mg/kg	Intravenous	Not described	
	Ketamine	NMDA antagonist	1–2 mg/kg	Intravenous, intrarectal, intramuscular	Bupropion- lowers seizure threshold	
	Benzodiazepines *Midazolam* *Diazepam*	GABA activation	0.02 mg/kg (intravenously) 0.4–0.8 mg/kg (orally) 5–15 mg (intravenously) 5–10 mg (intramuscularly)	Intravenous, oral, intramuscular	Not described	
	Dexmedetomidine	Alpha 2 receptor agonist	2.6–4 mcg/kg (orally) 1–2 mcg/kg (intranasal) 0.3–0.7 mcg/kg/h (intravenously)	Oral, intranasal, intravenous	Not described	
Inhalational anesthetics	Nitrous oxide	Not known	MAC 104		Not described	
	Sevoflurane		MAC 1.85–2		Phenothiazines—cardiotoxicity (prolonged QTc)	
	Isoflurane		MAC 1.15		Phenothiazines—cardiotoxicity (prolonged QTc) Fluoxetine—cardiotoxicity (prolonged QTc)	
	Desflurane		MAC 6		Not described	
	Enflurane		MAC 1.63		Phenothiazines—cardiotoxicity (prolonged QTc) TCA—cardiotoxicity (prolonged QTc) and seizures	
	Methoxyflurane		MAC 0.16		Not described	

Local anesthetics	Aminoesters *Procaine* *2-Chloroprocaine* *Tetracaine* *Cocaine* Aminoamide *Lidocaine* *Mepivacaine* *Prilocaine* *Bupivacaine* *Ropivacaine*	Block the transmission of the action potential by inhibition of voltage-gated sodium ion channels	Variable	Subcutaneous, perineural, intravenous	Not described	Local anesthetics can induce CNS toxicity if elevated plasma concentrations Excitatory symptoms (tremors, seizures), CNS depression (coma)
Opioids	Alfentanyl Fentanyl Sufentanyl Remifentanil Morphine Hydromorphone Meperidine	Inhibitory effects through binding of opioid receptors	Variable dosing taking into consideration surgical time, type of surgery, whether anesthesia, analgesia, or sedation are the desired effects	Oral, intravenous, intramuscular	Serotoninergic agents—increased risk of serotonin syndrome	*All opioids potentiate CNS depression associated with psychotropic medications* If patients with renal failure, normeperidine (active metabolite of meperidine) can cause myoclonus and seizures
Muscle relaxants	Succinylcholine Mivacurium Atracurium Cisatracurium Rocuronium Vecuronium Pancuronium	Direct binding of the acetylcholine receptors in the neuromuscular junction	1 mg/kg 0.25 mg/kg 0.4–0.5 mg/kg 0.1 mg/kg 0.6 mg/kg 0.1 mg/kg 0.1 mg/kg	Intravenous, intramuscular	Not described	

Table 5.2 Psychotropic medications

Drug class	Generic name	Trade name
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine Paroxetine Sertraline Fluvoxamine Citalopram Escitalopram	Prozac Paxil Zoloft Luvox Celexa Lexapro
Tricyclics (TCAs)	Amitriptyline Nortriptyline Clomipramine Imipramine Desipramine Protriptyline Doxepin	Elavil Pamelor Anafranil Tofranil Norpramin Vivactil Sinequan, Silenor
Monoamine oxidase inhibitors (MAOIs)	Phenelzine Tranylcypromine Isocarboxazid Selegiline Moclobemide	Nardil Parnate Marplan Emsam
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Duloxetine Venlafaxine Desvenlafaxine Levomilnacipran	Cymbalta Effexor Pristiq Fetzima
Atypical antidepressants	Bupropion Amoxapine Mirtazapine Trazodone Vilazodone Vortioxetine	Wellbutrin Asendin Remeron Desyrel Viibryd Trintellix

recommended that these agents be continued throughout the perioperative period with the exception of MAOIs, as discussed below.

Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs are the most commonly prescribed antidepressants in the USA. As their name suggests, they inhibit the neuronal reuptake of serotonin (5-HT) from the synaptic cleft. SSRIs are widely used for their proven efficacy and improved tolerability compared with older agents such as TCAs. SSRIs have nominal anticholinergic effects (except paroxetine) and very rarely cause cardiovascular side effects such as changes in cardiac conduction. Further, they are less sedating than TCAs and substantially safer than TCAs in overdose. SSRIs may cause mild, typically transient gastrointestinal side effects such as nausea, vomiting, and diarrhea as well as central effects including sleep disturbance, irritability, tremor, headache, and sexual dysfunction. SSRIs require several considerations for use in the perioperative period.

Serotonin Syndrome

Serotonin syndrome is a potentially life-threatening drug reaction that results from increased synaptic 5-HT levels in the brainstem and spinal cord. This can occur due to the combination of multiple drugs that promote serotoninergic activity (e.g., MAOIs, TCAs, meperidine, tramadol, dextromethorphan, herbs such as ginseng or *H. perforatum* commonly known as St. John's wort) or with overdose of a serotonergic agent [4]. Some opioids, including fentanyl and methadone, have serotonergic activity and may carry a risk of causing serotonin syndrome when used in conjunction with other serotonergic agents [5–7] (see Box 1).

Box 1: Medications Associated with Serotonin Syndrome

Amphetamines and derivatives: 3,4-methylenedioxymethamphetamine (ecstasy), dextroamphetamine, methamphetamine, sibutramine (Meridia)

Analgesics: fentanyl (Duragesic), meperidine (Demerol), tramadol (Ultram), cyclobenzaprine (Flexeril), pentazocine (Talwin)

Antibiotics: linezolid (Zyvox), ritonavir (Evotaz)

Antidepressants/mood stabilizers: buspirone (BuSpar), lithium, MAOIs (e.g., phenelzine), SSRIs (e.g., fluoxetine), serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine), serotonin 2A receptor blockers (e.g., trazodone), St. John's wort (*Hypericum perforatum*), TCAs (e.g., amitriptyline, nortriptyline)

Antiemetics: metoclopramide (Reglan), ondansetron (Zofran), granisetron (Sancuso, Granisol)

Antimigraine drugs: ergot alkaloids
Anticonvulsants: valproate (Depakote, Depakene)
Bariatric medications: sibutramine (Meridia)
Dietary supplements: ginseng
Drugs of abuse: ecstasy, lysergic acid diethylamide (LSD), foxy methoxy, Syrian rue
Over-the-counter cough medicine: dextromethorphan (Robitussin, Zicam, Delsym)

Serotonin syndrome is commonly identified by the triad of altered mental status or behavior (agitation, delirium, confusion), excessive neuromuscular activity (myoclonus, muscle rigidity, hyperreflexia, and clonus), and autonomic instability (hyperthermia, tachycardia, labile blood pressure, and diarrhea) caused by excessive 5-HT in the central nervous system and periphery. Seizures, rhabdomyolysis, renal failure, arrhythmias, coma, and death may also occur. Although very similar to neuroleptic malignant syndrome (NMS), serotonin syndrome more commonly presents with myoclonus and gastrointestinal symptoms than NMS. Supportive therapies are required to treat hyperthermia and autonomic dysfunction. Although most cases improve with symptomatic and supportive care, severe cases of serotoninergic syndrome may require intensive care including mechanical ventilation. Cyproheptadine (a 5-HT2A antagonist) is the most commonly administered serotonergic antagonist but is available only in an enteral formulation [8–11]. In patients on scheduled doses of serotonergic agents preoperatively, it may be reasonable to avoid meperidine, methadone, tramadol, fentanyl, and derivatives in order to minimize the risk of syndrome [5]. In such patients, opioids that do not enhance 5-HT activity (e.g., morphine, hydromorphone, codeine, oxycodone, buprenorphine) may be a safer choice for analgesia [5].

Discontinuation Syndrome

Abrupt cessation of antidepressants can cause a discontinuation syndrome ranging from mild to severe, with common features including nausea, abdominal pain, diarrhea, sleep disturbances (insomnia, vivid dreams, and nightmares), diaphoresis, headache, anxiety, and irritability. This syndrome has been best described with SSRIs, but similar syndromes can occur with abrupt cessation of any antidepressant. Gradual taper off antidepressants are often recommended to mitigate these symptoms [12].

Perioperative Bleeding

SSRIs decrease platelet aggregation at higher doses and may increase the risk of surgical bleeding, especially in combination with nonsteroidal anti-inflammatory drugs (NSAIDs). In patients undergoing procedures with a high risk of bleeding (neurosurgery, cardiac, vascular, spinal), patients on SSRIs may have higher rates of transfusion without affecting mortality [13, 14].

Additional Considerations

Several SSRIs inhibit hepatic cytochrome P450 isoenzymes, which can cause increased levels of other drugs including anesthetic agents leading to serious side effects (Table 5.3). CYP 2D6, in particular, converts codeine to morphine and also participates in the conversion of oxycodone and hydrocodone to their active metabolites, oxymorphone and hydromorphone, respectively [15]. Patients on certain SSRIs (fluoxetine, paroxetine, or sertraline) may therefore not achieve intended analgesia from these prodrugs due to a reduced ability to convert these to active metabolites. One final consideration with SSRIs is that they may cause the syndrome of inappropriate ADH secretion (SIADH).

Overall, the risks associated with continuation of SSRIs through the perioperative period are generally of limited clinical significance aside from the need to avoid other serotonergic agents and minding a few key potential drug-drug interactions. Given the risk of discontinuation syndrome and depression relapse with abrupt SSRI discontinuation and the relative safety of SSRIs,

Table 5.3 P450 isoenzymes and drugs whose metabolism is affected by inhibition or induction

P450 isoenzyme	Inducers	Inhibitors	Anesthetic medications affected
CYP1A2	Carbamazepine	Fluvoxamine	Acetaminophen Ropivacaine (local anesthetic) Ondansetron (antiemetic)
CYP2B6	Carbamazepine		Ketamine Narcotics (meperidine, methadone) Propofol
CYP2E1	–	–	Inhalational anesthetics
CYP2D6		Bupropion Citalopram Clomipramine Desipramine Duloxetine Escitalopram Fluoxetine Fluphenazine Fluvoxamine Haloperidol Moclobemide Paroxetine Perphenazine Risperidone Sertraline Thioridazine Valproic acid Venlafaxine	Narcotics (codeine, methadone)
CYP2C9	Carbamazepine	Fluvoxamine Paroxetine Sertraline	Non steroidal anti-inflammatory drugs (NSAIDs)
CYP2C19	Carbamazepine St John's wort	Fluoxetine Fluvoxamine Oxcarbazepine	Diazepam Lidocaine Tramadol Antiemetics (metoclopramide, ondansetron)
CYP3A4	Carbamazepine	Fluoxetine Fluvoxamine Nefazodone Paroxetine Sertraline Valproic acid	Acetaminophen Benzodiazepines (midazolam, diazepam, alprazolam) Narcotics (alfentanil, codeine, fentanyl, methadone) Lidocaine Antiemetics (ondansetron)

they are typically continued perioperatively without complication. In patients undergoing high-risk bleeding procedures or in patients on additional coagulation altering medications, tapering several weeks in advance or changing the antidepressant regimen may be considered.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Duloxetine is an SNRI with a small inhibitory effect on dopamine reuptake. Duloxetine is commonly used to treat major depressive disorder, generalized anxiety disorder, neuropathic pain, fibromyalgia, and chemotherapy-induced neuropathy. Nausea, somnolence, insomnia, and dizziness are its most common side effects, which are reported by 10–20% of patients. Duloxetine can be continued in the perioperative period, with the same general precautions as used for SSRIs [5].

Venlafaxine/desvenlafaxine are SNRIs that exhibit no significant effect on alpha-adrenergic, cholinergic, or histamine receptors. Because venlafaxine does not alter P450 enzymatic activity, no significant drug interactions with anesthetic drugs are described. They are typically continued perioperatively without consequence, though care should be taken with concurrent serotonergic agents.

Levomilnacipran is an SNRI with an especially high ratio of norepinephrine blockade to serotonin blockade. Side effects include nausea, dizziness, insomnia, tachycardia, and hypertension. It has recently been found to inhibit beta-site amyloid precursor protein cleaving enzyme-1 (BACE-1), responsible for β-amyloid plaque formation, and has been considered as a potential agent for treating Alzheimer disease. As with other SNRIs, it can be continued throughout the perioperative period, keeping in mind its possible interaction with serotoninergic agents [16].

Tricyclic Antidepressants (TCAs)

TCAs are used in the treatment of depression, neuropathic pain, nocturnal enuresis, migraine, and several other conditions. Their mechanism of action involves competitive inhibition of the reuptake of the amines norepinephrine and 5-HT from the synaptic cleft, thereby increasing the concentration of these transmitters in the synapse.

TCAs also exhibit muscarinic, histaminic, and alpha-adrenoceptor antagonism. The effects of anticholinergic activity include tachycardia, dry mouth, blurred vision, urinary retention, and constipation. Alpha-adrenoceptor blockade can cause postural hypotension. Sedation can be due to blockade of all three types of receptors. Overall, the most common side effects of TCAs are sedation and fatigue. TCAs can also cause ECG alterations including changes in the T wave, prolongation of the QRS complex, bundle branch block, or other conduction abnormalities such as a prolonged QTc and premature ventricular contractions (PVCs) [17].

TCAs are highly protein-bound; therefore, their effects may be enhanced by drugs that have a similarly high protein-bound fraction and in protein-deficient states. Metabolism occurs in the liver and often results in active metabolites. In overdose, TCAs are highly toxic. Severe effects include cardiotoxicity/arrhythmogenicity due to an increased QTc, convulsions (seizures), and coma ("the three Cs") as well as death. Treatment is supportive, often requiring intensive care. Administration of intravenous sodium bicarbonate to alkalinize the urine has been shown to be an effective treatment for resolving the metabolic acidosis and cardiovascular complications of TCA poisoning.

Anesthesia for a Patient on TCAs

TCAs should be continued during the perioperative period because discontinuing these agents can precipitate discontinuation symptoms or worsen the psychiatric or neurological illness for which they are being used. However, vigilance is required to minimize adverse effects resulting from increased sensitivity to catecholamines. Hypertension and arrhythmias may result from the use of sympathomimetic drugs (e.g., epinephrine and norepinephrine) and indirectly acting sympathomimetics (e.g., ephedrine, metaraminol), so these drugs should be avoided. Anesthetic drugs known to increase circulating catecholamines (ketamine, pancuronium, and meperidine) act as sympathomimetics and should be used with caution. There is a risk of ventricular arrhythmias in patients who develop hypercapnia while receiving volatile agents (particularly halothane). TCAs may result in increased response to intraoperatively administered anticholinergics, and agents that cross the blood-brain barrier, such as atropine, may cause postoperative confusion. TCAs can also potentiate CNS depression in combination with other CNS depressants such us barbiturates, benzodiazepines, and opioids. Moreover, in patients on chronic TCA treatment, catecholamine stores may be depleted resulting in cardiac depression and hypotension in the perioperative period.

Despite these considerations, TCAs are more often than not continued perioperatively, especially in patients with no underlying cardiac disease. In patients where arrhythmias may be of concern, it may be safer to taper off TCAs slowly to avoid withdrawal [18].

Monoamine Oxidase Inhibitors (MAOIs)

Whereas MAOIs were among the first drugs to be used in the treatment of depression, they are nowadays commonly restricted to treatment-resistant depression due to the high incidence of side effects and dietary restrictions they require. MAOIs work by binding irreversibly to the enzyme monoamine oxidase (MAO), which is present on external mitochondrial membranes, to inhibit its activity. This causes an increase in intraneuronal levels of amine neurotransmitters, which is thought to mediate their antidepressant and anti-narcoleptic effects and, in the case of selegiline, the possible benefit in delaying progression of Parkinson disease.

There are two forms of MAO—MAO-A and MAO-B. MAO-A metabolizes epinephrine, norepinephrine, and serotonin, and MAO-B preferentially metabolizes nonpolar aromatic amines such as phenylethylamine and methylhistamine. Dopamine and tyramine (a precursor of noradrenaline which is found in aged cheese, cured meats, pickled herring, chicken liver, chocolate, and other foods) may be metabolized by either subtype. MAO-A is the main form found in the human brain, but systemically MAO-B is responsible for 75% of MAO activity and found predominantly in the gastrointestinal tract, platelets, and most other non-neural sites.

In patients taking MAOIs, indirect-acting sympathomimetics (e.g., ephedrine, metaraminol) are contraindicated due to the potential for severe hypertensive reaction. Direct-acting sympathomimetics (e.g., phenylephrine) are preferred if needed perioperatively. The majority of inhalational and intravenous anesthetics are safe in these patients with the exception of ketamine, which can exacerbate the sympathetic response [19].

Anesthesia for a Patient on MAOIs

Because there are numerous potential interactions between MAOIs and anesthetic agents, the traditional recommendation has been to discontinue an MAOI 2–3 weeks before any planned procedure or elective surgery to allow regeneration of the enzyme. However, discontinuing MAOI places a patient at risk of a discontinuation syndrome and, critically, recurrence of depressive symptoms. Because patients on MAOI usually have severe underlying depressive illness including a risk of suicide, discontinuing them should be approached with great caution. Generally, preprocedural discontinuation is discouraged, but the final decision as to whether to discontinue MAOI therapy preoperatively should be made in advance on an individual basis, after careful discussion between the anesthesiologist, psychiatrist, and the patient. Although continuation of MAOI carries risks, careful anesthetic technique can minimize these. Ultimately, these risks should be balanced against the risk of depressive relapse and discontinuation symptoms.

When an MAOI is discontinued, it should be for the minimum period, with gradual reduction of dose and under psychiatric supervision. Treatment should be restarted as soon as possible postoperatively. Moclobemide, a reversible inhibitor of MAO-A approved for use outside the USA, is unique among MAOIs because it is a reversible MAOI, which can generally be discontinued 24 h before surgery without complications. Selegiline is relatively selective for MAOI-B at lower doses and does not need to be stopped if taken at doses <10 mg/day. At this dose the risk of interaction with sympathomimetics is minimal. Meperidine should be avoided in combination with any dose of selegiline. Neuraxial anesthesia is not contraindicated on patients taking MAOIs, but care must be taken in treating hypotension as described above.

If continued on MAOI, the patient should be prescribed a tyramine-free diet preoperatively to avoid precipitating a hypertensive crisis [19–21]. In addition, the patients on continued MAOI and those who require emergent procedures require close hemodynamic monitoring for early diagnosis of complications and prompt treatment of adverse reactions such as serotonin syndrome. The following steps should be taken to minimize risks:

1. Avoid sympathetic stimulation. Consider premedication with sedatives such as benzodiazepines.
2. Provide adequate intravascular volume and avoid dehydration.
3. Treat hypotension initially with intravenous fluids and then with cautious doses of phenylephrine (e.g., 25–50 mcg) to evaluate the effect.
4. Ephedrine, metaraminol, and meperidine are absolutely contraindicated.

Potential interactions in the perioperative period are described below:

- *Intravenous induction agents*: MAOIs may cause a reduction in the hepatic metabolism of barbiturates, requiring a dose reduction in sodium thiopental. Propofol and etomidate can be used safely, but ketamine should be avoided because it can exacerbate the sympathetic response [19].
- *Opioids*: There are two different reactions that can occur between MAOIs and opioids. In patients taking dextromethorphan and MAOI, an excitatory or type I reaction, similar to serotonin syndrome, can occur. This is characterized by sudden agitation, headache, hyper- or hypotension, myoclonus, hyperthermia, seizures, and coma [22, 23]. However, opioids like morphine, fentanyl, alfentanyl, and remifentanil can all be used safely. A rare depressive, or type II reaction, due to MAO inhibition of hepatic enzymes resulting in enhanced effects of all opioids, leads to excessive oversedation. Therefore, this reaction is reversed by naloxone [19].
- *Neuromuscular blocking agents*: Phenelzine decreases plasma cholinesterase concentration and therefore prolongs the action of succinylcholine. This does not occur with other MAOIs. Pancuronium should be avoided with MAOIs as it releases stored norepinephrine. Other muscle relaxants can be used safely in patients taking MAOIs.
- *Sympathomimetics*: The indirect sympathomimetics ephedrine and metaraminol may precipitate serious hypertensive crises and are absolutely contraindicated with any MAOI. The direct-acting sympathomimetics (epinephrine, norepinephrine, and phenylephrine) should be cautiously titrated to effect in patients taking MAOIs as they may have an enhanced effect due to receptor hypersensitivity [19].
- *Local anesthetics*: Except for cocaine, all ester and amide local anesthetics can be used safely with MAOIs, but special care should be taken with preparations containing epinephrine. Other drugs used in the perioperative period, such as benzodiazepines, inhalational anesthetic agents, anticholinergics, and NSAIDs, can all be used safely in patients taking MAOIs.

Atypical Antidepressants

Mirtazapine is a norepinephrine and selective serotonin antagonist that increases amine release from nerve endings by blocking presynaptic alpha-2 adrenoceptors and postsynaptic serotoninergic receptors. It also has potent antihistaminic effects, which combine with serotonin blockade to cause sedation and weight gain. Mirtazapine does not have significant effects on blood pressure or heart rate. Mirtazapine can be continued during the perioperative period as its risk is comparable to that of SSRIs.

Bupropion selectively inhibits neuronal reuptake of catecholamines (norepinephrine and dopamine) and has minimal effect on serotonin reuptake. It does not inhibit either form of monoamine oxidase. While no literature exists regarding perioperative management of bupropion, it can lower seizure threshold when ketamine is used.

Amoxapine is a tetracyclic antidepressant that inhibits the reuptake of serotonin and norepinephrine. Amoxapine may deplete catecholamine reserves in nerve terminals by blocking norepinephrine reuptake into presynaptic nerve terminals and downregulate postsynaptic adrenergic receptors due to exposure to high concentrations of norepinephrine produced by reuptake inhibition. Therefore, it has been suggested to discontinue amoxapine 24 h before an operation to improve the responsiveness of alpha-adrenoceptors [24].

St John's wort (*Hypericum perforatum*) is a popular herbal medicine used for mild depression. The extract derived from this plant contains several alkaloids with similar structure to TCAs and may induce cytochrome P450 enzymes CYP3A4 and CYP1A2, resulting in altered metabolism of several drugs used in the perioperative period. Agents that may require closer monitoring as a result include certain local anesthetics (lidocaine), analgesics (alfentanyl, fentanyl, methadone), sedative agents (midazolam, diazepam), and the antiemetic ondansetron [25].

Mood Stabilizers

Bipolar disorder, occasionally called manic-depressive illness, is characterized by discrete mood episodes that cause clinically significant distress or impairment. Its diagnosis requires the presence of either a manic or hypomanic episode. Virtually all patients with bipolar disorder will have lifetime depressive episodes as well. Mood stabilizers such us lithium and anticonvulsant drugs are the standard of care for managing bipolar disorder. During the perioperative period, mood stabilizers should not be discontinued abruptly as there is a significant risk of mood relapse.

Lithium

Lithium is widely considered the gold-standard agent in managing bipolar disorder. It has proven efficacy in treating manic and depressive episodes as well as for bipolar maintenance to prevent mood episode relapse. Its exact mechanism of action is unknown. It mimics the action of sodium in the membranes of neuronal cells and decreases the release of excitatory neurotransmitters (dopamine and glutamate) and increases inhibitory neurotransmission (GABA).

It has a relatively low therapeutic index, so plasma levels should be monitored closely, especially during the first few weeks of treatment. Although earlier recommendations suggested that levels from 0.8 to 1.2 mEq/l were necessary for effect, especially for acute stabilization, modern evidence and current recommendations broadly recommend levels of 0.4–0.8 mEq/l for both acute stabilization and maintenance. Plasma levels above 1.5 mmol/l generally indicate toxicity, which manifests as nausea, vomiting, altered level of arousal (either lethargy or restlessness/agitation), polydipsia, polyuria, ataxia, and hypokalemia. In severe cases, renal failure, convulsions, coma, and death can occur with increasing serum levels. The management of lithium toxicity is supportive and includes seizure control, hydration, and correction of electrolyte abnormalities.

Hemodialysis is the most effective method for clearing lithium in the extracellular compartment and is the treatment of choice if the patient is hemodynamically stable. Continuous veno-venous hemodialysis/filtration (CVVHD/CVVHDF) may be better tolerated by patients with hemodynamic instability. Renal replacement therapy is indicated at any lithium concentration if the patients exhibit low levels of consciousness, seizures, or life-threatening complications, with lithium level > 4 mEq/l in patients with decreased creatinine clearance (creatinine > 2 mg/dL) or any patient with lithium level > 5 mEq/l [26].

Anesthesia for Patients on Lithium

Lithium can be continued in the context of minor surgery. Some authors have suggested that lithium should be stopped 24–48 h before major surgery, but this suggestion is controversial. From a psychiatric perspective, interruptions in lithium therapy may be disastrous for the patient because lithium discontinuation can precipitate mood episode relapse. Because lithium is excreted exclusively by the kidneys, drugs that may impair renal function should be used with caution, including NSAIDs which may also increase lithium levels (*n.b.*, as an exception, the NSAID aspirin does not affect lithium excretion). Careful attention should be paid to fluid and electrolyte balance. If discontinued prior to surgery, lithium should be restarted 24 h after surgery.

Lithium can interfere with several anesthetic agents. Centrally, it may reduce anesthetic requirement because it blocks brainstem release of noradrenaline and dopamine. Lithium may also prolong the duration of neuromuscular blockade produced by both depolarizing and non-depolarizing neuromuscular blockers, an effect that may be due to lithium-induced inhibition of acetylcholine synthesis and release at the neuromuscular junction as well as competition with sodium ions during depolarization events. Therefore, the dose of neuromuscular blocker may often be reduced in patients on lithium therapy, and use of nerve stimulator intraoperatively should be strongly considered [27, 28].

Divalproex, *valproic acid*, or *valproate* (Depakene, Depakote) are used both as a prophylactic agent in bipolar disorder and to treat acute mania. Possible side effects include nausea, gastric irritation, diarrhea, weight gain, hyperammonemia, thrombocytopenia, and rarely pancreatitis. Valproate is highly protein-bound and, therefore, may displace other protein-bound drugs such as warfarin, leading to increased therapeutic levels and possible toxicity. The vast majority of valproate metabolism occurs in the liver (by the cytochrome P450 enzymes CYP2A6, CYP2B6, CYP2C9, and CYP3A), and increased levels may occur when given concomitantly with enzyme inhibitor drugs. About 50% of an administered dose of valproate is excreted in urine as a glucuronide conjugate. The other major pathway in the metabolism of valproate is mitochondrial beta-oxidation. Valproic acid confers resistance to non-depolarizing muscle relaxants (e.g., rocuronium, vecuronium).

Carbamazepine (Equetro, Tegretol) is an anticonvulsant medication used in the maintenance of bipolar disorder. Among its side effects include dizziness, drowsiness, ataxia, and nausea. Carbamazepine is a potent inducer of hepatic enzymes—especially CYP3A4 and CYP3A5—and therefore reduces the plasma levels of many anesthetic drugs including benzodiazepines. It may cause chronic leukopenia, hyponatremia, agranulocytosis, aplastic anemia, or a hepatic picture with elevated liver enzymes.

Oxcarbazepine (Trileptal) is an anticonvulsant primarily used in the treatment of epilepsy and only occasionally as a mood stabilizer. Common side effects include nausea, vomiting, dizziness, drowsiness, headache, diplopia, ataxia, and hyponatremia [29]. Oxcarbazepine induces CYP3A4 and CYP3A5, and its metabolite inhibits CYP2C19; as such, it has been shown to influence the metabolism of a broad range of other medications including citalopram, diazepam, imipramine, propranolol, amitriptyline, and dihydropyridine calcium channel blockers.

Lamotrigine is an anticonvulsant (sodium channel-blocking class) and an effective mood stabilizer, used for maintenance treatment of bipolar disorder. It does not need to be discontinued in patients undergoing anesthesia.

Typical and Atypical Antipsychotics (Neuroleptics)

Antipsychotics are most commonly used to treat patients with schizophrenia, schizoaffective disorder, and bipolar disorder, but many agents have other psychiatric applications as well including as adjuncts for major depressive disorder and irritability in autism spectrum disorder. Antipsychotics may also occasionally be used for somatic symptoms such as nausea and vomiting. They are classified into two groups:

1. *Typical antipsychotics*: These include the low-potency agents chlorpromazine (Thorazine) and thioridazine (Mellaril); "mid-potency" agents perphenazine (Trilafon), thiothixene (Navane), and trifluoperazine (Stelazine); and the high-potency agents haloperidol (Haldol), fluphenazine (Prolixin), and pimozide (Orap). Two additional agents with similar pharmacodynamics activity used primarily as antiemetics include metoclopramide (Reglan) and prochlorperazine (Compazine).

   - Typical antipsychotics may cause a variety of side effects. Extrapyramidal symptoms including acute dystonia, akathisia, or parkinsonism are due to a dopamine receptor blockade in the substantia nigra. Dopamine blockade in the area postrema is postulated to mediate their antiemetic effects. Anticholinergic effects are very common with low-potency agents as is sedation due to a combination of anticholinergic and antihistaminic activity. Further, alpha-1 adrenergic antagonism caused by low-potency agents may contribute to orthostatic hypotension. Several ECG abnormalities have been described with antipsychotics including QT or PR interval prolongation, blunting of T waves, ST segment depression, and, rarely, PVCs and torsades de pointes.

- In the perioperative period, inhalational anesthetics and phenothiazines both prolong the QTc interval, placing these patients at risk for arrhythmias.

2. *Atypical antipsychotics*: The more commonly encountered among these include clozapine, olanzapine, risperidone, quetiapine, and aripiprazole. Atypicals similarly exhibit D2 receptor blockade but cause less extrapyramidal side effects, which is thought to be due to the modulatory effect of their concurrent 5-HT2 receptor antagonism. In addition, they have effects on other receptors including histamine (H1), acetylcholine (muscarinic), and alpha-adrenergic receptors. Clozapine is notable for lowering seizure threshold, carrying a risk of fatal cardiopulmonary suppression, and potentially causing either myocarditis or agranulocytosis [30].

Neuroleptic Malignant Syndrome (NMS)

NMS is an uncommon, idiosyncratic reaction to antipsychotics characterized by acute hyperpyrexia, muscle rigidity, and autonomic instability. Creatinine kinase and white cell count are usually very elevated. This syndrome may be life-threatening, with a mortality rate up to 20%. Patients with NMS should be treated in a critical care setting. The muscle relaxant dantrolene and the dopamine agonist bromocriptine may be used along with supportive treatment. Despite the similarities in clinical presentation with malignant hyperthermia, there is no proven association between the two conditions [19].

Anesthetic Considerations for Patients Taking Antipsychotic Drugs

Antipsychotic medication should generally be continued perioperatively. Where these agents are being prescribed for psychotic illness, abrupt discontinuation may result in recurrence of psychotic symptoms and increased incidence of postoperative confusion if antipsychotics are stopped <72 h prior to the surgical procedure [31]. Antipsychotics potentiate the hypotensive and sedative effects of general anesthetic agents; thus, special precaution should be taken with anesthesia [31, 32]. Temperature regulation may be impaired due to dopamine blockade on the hypothalamus [33]. Patients on antipsychotic medication appear to be less sensitive to postoperative pain [34]. Dysregulation of N-methyl-d-aspartate (NMDA) receptor transmission in patients with schizophrenia may account for pain insensitivity coupled with analgesic effects of most antipsychotics [34].

Neuroleptic agents may place patients at a higher risk of developing postoperative paralytic ileus. This risk is thought to be due to sympathetic hyperactivity and can be reduced by epidural analgesia. Patients on these agents may also be at increased risk of water intoxication due to elevated secretion of ADH. An increased risk of sudden death has been reported, likely in the setting of phenothiazine overdose perioperatively leading to cardiotoxicity [32].

Benzodiazepines

Anxiety disorders such as generalized anxiety disorder, panic disorder, and social anxiety disorder are very common, and although SSRIs tend to be first line for managing these, benzodiazepines are often used as adjuncts to treat these anxiety disorders. Benzodiazepines are also used to treat anxiety in other psychiatric conditions and may be used as muscle relaxants and hypnotics or to treat akathisia. Where benzodiazepines are used chronically, they should be continued through the perioperative period in order to avoid physiological withdrawal.

Benzodiazepines are frequently used in the medical hospital as anxiolytics, sedatives, and hypnotics. They exert their action as positive allosteric modulators of GABA receptors, which are the key targets that mediate most clinically important effects of IV anesthetics. In the clinical practice of anesthesia, midazolam is used immediately before induction of anesthesia for anxiolysis as a premedication. The other agents, diazepam and lorazepam, are used occasionally.

Midazolam is metabolized by CYP3A4 and CYP3A5 to its main metabolite 1-hydroxymidazolam and minor metabolites 4-hydroxymidazolam and 1,4-hydroxymidazolam. Diazepam's metabolism occurs in the liver and is mediated mainly by CYP2C19 and CYP3A4. This accounts for 80% of the biotransformation of diazepam. The active metabolite nordazepam, common to diazepam and chlordiazepoxide, has a half-life of >96 h and often accumulates with repeated doses. Lorazepam is conjugated both in the liver and extrahepatically to an inactive glucuronide. This metabolite is water soluble and rapidly excreted in urine.

All benzodiazepines have hypnotic, sedative, anxiolytic, amnestic, anticonvulsant, and centrally produced muscle-relaxing properties with escalating doses. However, they differ to some extent in their potency and efficacy with regard to each of these properties. In terms of relative dose equivalence, midazolam is approximately 3–6 times, and lorazepam 5–10 times, as potent as diazepam.

The inhibition of CYP3A by concomitantly administered drugs such as the azole antifungal agents (among many others) results in significant inhibition of the metabolism of midazolam. Orally administered midazolam is especially affected by these inhibitors because of a reduction of first-pass metabolism elimination. Diazepam is primarily metabolized by CYP2C19 and CYP3A4. Inhibitors of CYP2C19 such as fluvoxamine consequently increase the plasma half-life of diazepam substantially. The clearance of lorazepam is affected by valproic acid, which decreases the formation and clearance of lorazepam glucuronide.

Benzodiazepines act synergistically with opioids and intravenous anesthetics to cause CNS depression. The inhalational anesthetic requirements are decreased for patients receiving benzodiazepines acutely, whereas patients who take benzodiazepines chronically often require higher concentrations for maintenance of anesthesia.

Take-Home Points

- Except for MAOIs, antidepressants should generally be continued throughout the perioperative period to avoid discontinuation symptoms. Their use in this context typically entails marginal, if any, increased risk of complications.
- Serotonin syndrome is a potentially lethal condition that occurs when serotonergic agents are combined or, occasionally, in overdose on a single agent. Two common analgesics that can precipitate serotonin syndrome in patients on serotonergic antidepressants are tramadol and meperidine.
- Careful perioperative planning is required for patients on MAOIs.
- Meperidine and the indirectly acting sympathomimetics ephedrine and metaraminol are absolutely contraindicated in patients on MAOIs.
- Moclobemide is a reversible inhibitor of MAO-A and has a better safety profile in combination with comment agents given in the perioperative setting than traditional MAOIs.
- Mood stabilizers and antipsychotic drugs should be continued throughout the perioperative period to minimize the risk of symptom relapse.
- Lithium has a low therapeutic index, so levels should be monitored closely throughout perisurgical care.
- Patients taking lithium require special care with fluids and electrolytes in the perioperative period. Medications that may cause renal injury should be avoided where possible.

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6

Psychiatric Aspects of Perioperative Pain

Teofilo E. Matos Santana

Introduction

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage [1]. Postoperative pain is the acute pain experienced after a surgical procedure. Estimates suggest that more than 80% of the patients will experience postoperative pain; among these patients, most will rate their pain as moderate or severe immediately after surgery, and up to 75% will still have these levels of pain at the time of discharge [2–4].

Postoperative pain represents one of the principal fears for patients preparing for surgery [4]. When not managed well, it can lead to delayed functional recovery and increased risk of postsurgical complications including poor wound healing and myocardial ischemia [5, 6]; therefore, it is important to understand the assessment and management of postoperative pain.

Pain is one of the three most common medical causes of delayed discharge after ambulatory surgery, the other two being drowsiness and nausea/vomiting [6]. Even though fewer than half of the patients who undergo surgery report adequate pain relief [3], more than 80% of patients surveyed believe that postoperative pain is necessary and report being satisfied with pain management [3, 4].

This chapter has several aims: (1) to cover the definition and mechanism of acute postoperative pain in the adult patient, (2) to review the standard assessment of pain, (3) to outline the pharmacological and non-pharmacological management of postoperative pain, and (4) to discuss the management of postoperative pain in special populations including patients with chronic pain and patients with a substance use disorder (especially opioid use disorder).

Pain

Classification of Pain

Most commonly, pain is classified either according to its duration or its mechanism. Pain can be described in terms of duration as transient, acute, or chronic [7]. Transient pain is elicited by activation of receptors in the skin or other tissue in the absence damage; it is usually ubiquitous in daily life and rarely a clinical concern [8]. Acute pain is associated with acute tissue injury. This type of pain usually last for less than a month but may rarely persist for 3–6 months [9]. Acute pain is commonly associated with activation of sympathetic nervous system, producing tachycardia, diaphoresis, tachypnea, and observable distress [10]. Chronic pain is of longer duration,

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classically defined as more than 6 months. It persists after acute tissue injury has healed and is perpetuated by many factors beyond the original cause of pain [8].

Mechanistic subtypes of pain include nociceptive, inflammatory, and dysfunction/neuropathic. Nociceptive pain refers to the consequence of threatened or real tissue injury in which the primary sensory neurons respond to a noxious stimulus by ultimately activating the central nervous system. This type of pain has a protective function because it alerts the body to external threats (e.g., pinprick or heat) and internal threats (e.g., myocardial infarction) through exogenous and endogenous chemical mediators [11, 12]. Nociceptive pain occurs exclusively in the presence of a noxious stimulus.

Inflammatory pain refers to the response to tissue injury and subsequent inflammatory response. This type of pain alerts the body regarding a need to address the consequences of the initial damage [12, 13]. The inflammatory process increases the sensitivity of pain receptors causing activation by even innocuous stimuli [11]. Surgical incision and burns can lead to inflammatory pain. Inflammatory pain disappears after resolution of both the index tissue injury and the ensuing inflammatory state.

The third type of pain is dysfunctional pain, commonly called neuropathic pain, which is due to direct injury to nervous tissue resulting in long-term changes in the sensitivity of pain receptors [13]. This pain state is maladaptive because it neither protects tissue nor supports tissue healing and repair [11]. Diabetic peripheral neuropathy due to injury of long-tract peripheral nerves is a common example of this type of pain.

Physiology of Pain

Nociceptive messages are integrated at every level of the nervous system [14]. Specialized receptors in the skin or other tissues, called nociceptors, sense pain and provide information to the central nervous system (CNS). Nociceptors can be stimulated by mechanical, thermal, or chemical damage [7, 9]. The physiological process that converts a noxious stimulus into a neural impulse is called *transduction*. The nociceptive impulse is transmitted to the CNS by two types of neurons, the A-delta and C nerve fibers [14, 15]. A-delta fibers are fast conducting and transmit sharp injurious stimuli [13]. C fibers are slower conducting and are responsible for the dull, aching, and visceral types of pain [13]. These sensory neurons from the periphery enter the spinal cord and synapse with neurons in the dorsal horn, in a process known as *transmission*. The second-order neurons in the dorsal horn will continue to ascend with most decussating (i.e., crossing the midline to activate contralateral brain regions) in the anterior commissure and travel in the spinothalamic tract terminating in the thalamus. From the thalamus, pain impulses travel to the sensory cortex, where these higher centers are responsible for the conscious awareness of pain, also known as *perception* [13]. During the *perception* phase, the neurons comprising the spinothalamic tract course through the pons, medulla and midbrain to terminate in the thalamus, sending collateral branches to the reticular formation [7, 13]. The impulses transmitted via these tracts are responsible for the perception of pain. Activation of the reticular formation is theorized to generate the increased arousal and emotional components of pain.

This incoming sensory information is modulated by inhibitory and excitatory neuronal systems in the brain. The descending pathways including corticospinal tract and the hypothalamic efferents can modulate nociceptive transmission in the spinal cord by altering release of neurotransmitters such as serotonin, norepinephrine, and endorphins; or they can activate inhibitory pathways supraspinally through gamma-aminobutyric acid (GABA) and glycine [13, 14]. This process modifies the nociceptive transmission in the periphery, spinal cord, and encephalon. This process is known as *modulation*. Modulation occurs by way of alterations of neurotransmitter release (norepinephrine, serotonin, and endorphins) and activation of inhibitory pathways. GABA and glycine are important inhibitory neurotransmitters that act at the dorsal horn of spinal cord [13].

The postsurgical state is characterized by fat and muscle breakdown, hyperglycemia, and impaired immune function. Surgery causes an immunological and neuroendocrine reaction. The stress response to surgery involves the increased secretion of pituitary hormones and activation of the sympathetic nervous system. The activation of the sympathetic nervous system results in increased secretion of catecholamines from the adrenal medulla and release of norepinephrine from presynaptic nerve terminals. These changes produce the postsurgical perturbations that include increased plasma concentrations of peptide such as endorphins, the release of neurotransmitters such as catecholamines, and increased secretion of hormones such as cortisol, growth hormone, prolactin, and vasopressin [16].

Implications for Treatment

During the transduction process, pro-inflammatory substances are released from the damaged tissue-causing sensitization (i.e., reduction of nociceptive threshold) of the peripheral receptors. This increases pain transduction, causes neurogenic edema, and leads to hyperalgesia near the site of the injury [12, 15]. These processes contribute to the post-injury state of hypersensitivity seen in the postoperative patient [13]. The role of treatment in this stage is to prevent the release of the neurotransmitters that facilitate pain and to inactivate the inflammatory mediators. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase in the spinal cord and periphery, and they reduce the nociceptive response to endogenous mediators of inflammation [9, 15]. Acetaminophen and glucocorticoids treat inflammation because they are potent inhibitors of the metabolites of the arachidonic acid cascade as well as inhibitors of several of the metabolically active macrophage-derived peptides.

During the transmission phase in the dorsal horn, when the A-delta and C fibers synapse with the second-order neurons in the dorsal horn, several neurotransmitters are released including substance P and neurokinin, contributing to increased excitability. For instance, substance P induces the release of excitatory amino acids that activate AMPA and NMDA receptors, causing enhanced excitability and sensitization [12, 13, 15]. Mu and delta opioid agonists reduce the release of primary afferent neurotransmitters (e.g., substance P and glutamate) by C fibers. When stimulated, the postsynaptic opioid receptors hyperpolarize the membrane of dorsal horn neurons reducing activity in nociceptive pathways. Opioids also act peripherally by preventing nociceptor sensitization induced by inflammatory mediators. Opioids act peripherally on the injured tissue to reduce inflammation and centrally in the dorsal horn both to impede transmission of nociception and to activate inhibitory pathways that descend to the spinal segment [9].

When a C fiber stimulus is maintained with sufficient intensity and frequency, the NMDA receptor is activated, amplifying and prolonging the response as well as causing central hyperalgesia. NMDA antagonists like ketamine and dextromethorphan have an increasing role in the management of pain [9, 13]. Opioids and NMDA antagonists may be used synergistically, and the combination has shown benefits. Alpha-2 adrenergic receptor stimulation in the spinal cord and higher centers can exert a potent analgesic response as well; although its mechanism of action remains unclear, it is postulated to be related to the modulation of acetylcholine release [9, 13]. The effect of alpha-2 adrenergic agonists such as clonidine is short-lived but may be useful to augment morphine analgesia and to extend and intensify local anesthetic blocks [9]. Tricyclic antidepressants exert analgesic activity during the modulation phase by way of descending pathways that involve serotonin and noradrenaline [17].

Perioperative Pain Management

Preoperative

The management of perioperative pain ideally begins in the preoperative period and involves education and planning. This period is an opportunity to assist the patient in the decision-making process. Information about treatment options, goals of pain treatment, and pain expectation should be presented in a collaborative manner and individually tailored, especially to health literacy [18].

Preparation for surgery will include the adjustment or continuation of medications whose sudden cessation may provoke a withdrawal syndrome. Therefore, special attention should be given to benzodiazepines, opioids, barbiturates, gabapentin, and baclofen (*see* Chap. 5 for detailed discussion on the use of psychotropic medications in the perisurgical period).

During preoperative evaluation, the clinician should discuss recommended interventions to reduce preexisting pain and anxiety. Certain patients with medical complications and psychosocial stressors may need more support during the postoperative period and throughout recovery. Facilitating preoperative discussions about postoperative pain management, expectations, and available treatments have shown to reduce postoperative anxiety [19], opioid requirement [20], sedative demands, and even length of stay after surgery [18, 21]. Counseling should include information about how pain will be assessed, how and when it should be reported, and realistic goals of pain control [18]. This encounter is also important to address misconceptions about pain medications. Patients often believe that pain after surgery does not warrant treatment or that they will become addicted if they receive opioid treatment. The counseling and education should also involve the family and caregivers.

Depending on the type of surgery, there are specific guidelines for preoperative interventions aimed at improving the pain control after surgery. These interventions are typically incorporated in the anesthesia evaluation and management. Most of these guidelines recommend multimodal, opioid-sparing treatment plans to be used and implemented before the induction of anesthesia. These interventions are integrated in the preoperative preparation, together with other recommendations such as diet/NPO or medications to prevent nausea. Professional organizations update these guidelines periodically, according to new evidence. For the clinician providing mental health services in the perioperative settings, familiarity with these procedures is helpful to facilitate appropriate integration of all interventions, since psychotropic medications may interfere or duplicate agents used in pre-anesthesia [22, 23].

It is also important to assess for psychiatric comorbidities and substance use disorders because they can affect the patient's recovery. Anxiety and mood disorders can affect the perception of pain and impede postoperative recovery. Panic disorder and claustrophobia are two anxiety disorders that can be precipitated in the postoperative period especially if mobility is impaired, if the patient is connected to monitors, and if the respiratory system is compromised. The patient may present with psychological distress, insomnia, and irritability; these symptoms can increase the demand for pain medications or interfere with active participation in the recovery process. Assessment of cognitive status is also of great importance because cognitive deficits can alter the patient's ability to report pain, which can have a deleterious impact on recovery. Preoperative physiological dependence on opioids is often associated with increased opioid requirement after surgery and delayed recovery [24]. The presence of substance use disorders, especially opioid use disorder, requires the clinician to intervene to mitigate possible opioid misuse. These are all factors that will affect the choice of medication, follow-up, and monitoring [18].

Postoperative

Due to campaigns starting in the mid-1990s, pain has become commonly known as "the fifth vital sign," and it is routinely assessed in hospitals. There are many methods utilized for pain measurement including verbal rating scales, visual analogue scales, picture or face scales, and numerical rating scales that are both sensitive and easy to administer. Perioperatively, in addition to recording the subjective pain rating as elicited from the patient, the medical staff routinely evaluates the respiratory status and the level of sedation, to identify potential complications of pain medications. Immediately after surgery the clinician will need to perform regular reassessments to determine the adequacy of pain relief. It is also important to identify early possible complications post-surgery such as respiratory depression requiring an opioid dose reduction or opioid antagonist. It is recommended to assess the patient every 1–2 h, looking for changes in the depth and rate of respiration. There are multiple arousal/sedation scales that can be used to prevent problematic opioid-induced sedation. For instance, the Pasero Opioid-Induced Sedation Scale performs well clinically and is easy to use. Optimal pain management will require regular analgesic adjustments to prevent oversedation and ensure progress toward functional goals.

It is recommended to utilize a validated pain intensity scale and to assume a flexible approach to pain management. Because pain is a subjective experience, a patient's self-report is the primary basis of pain assessment. Patients with cognitive impairment, developmental disorders, or other factors that compromise an accurate report of pain such as a language barrier or cultural- and education-related factors will benefit from the use of behavioral assessment tools that infer pain levels and from soliciting caregiver input about pain levels [25].

Pain management in the postoperative setting that incorporates pharmacological and non-pharmacological interventions is usually most effective. Combining analgesic strategies—an approach known as *multimodal therapy*—is widely recommended and offers better pain management. The choice of which analgesic strategies to implement, though, will depend on a range of clinical and patient-related factors. Some examples include the nature of surgery and anticipated course of pain, type and severity of pain, and patient-specific factors including patient preference, history of analgesic use and response to such treatment, and kidney and liver function.

Multimodal Therapy

Multimodal analgesia is a well-established treatment option that involves multiple types of interventions to combat pain. It commonly combines both pharmacological and non-pharmacological treatments, and when multiple medications are used, they will typically have different, ideally synergistic, mechanisms of action and often different routes of administration based on pharmacokinetic considerations.

High-quality evidence supports the use of multimodal analgesia for the treatment of postoperative pain. It has been shown to reduce pain scores, total analgesic use, and in some cases, even length of hospital stay [6, 26]. In fact, combining interventions often offers additive or synergistic effects, resulting in more effective pain relief compared with single interventions [18, 27]. For instance, an NSAID combined with intravenous patient-controlled morphine administration may decrease nausea and sedation in patients when compared to using morphine alone [27]. Additionally, non-pharmacologic approaches including physical and psychological interventions consistent with the biopsychosocial model of pain provide multiple benefits [18]. The specific interventions chosen for a given patient will vary depending on type of surgery, patient preference, and availability of resource in the medical center. When using multimodal analgesia, clinicians should be mindful of the side effects and possible medication interactions including, for instance, the risk of bleeding or kidney injury with NSAIDs or hepatotoxicity with acetaminophen.

Pharmacological Analgesia

Opioids

Opioids are the mainstay for treating acute, moderate-to-severe pain in the postoperative period. They bind opioid receptors in the central and peripheral nervous system modulating the effect of the injury in the nociceptors. Some of the more common opioids include morphine, hydromorphone, and fentanyl (see Table 6.1) [28].

Route The oral route is recommended over the intravenous (IV) for the management of postoperative pain. Evidence suggest that IV administration of opioids is not superior to oral administration [29]. Experts recommend against the intramuscu-

Table 6.1 Overview of opioids

	Brand name	Morphine equivalents	PO:IV	Parental dose	Oral dose	Duration of action (h)	Enzyme	Metabolites	Side effects	Notes
Phenanthrenes										
Naturally occurring										
Morphine		1	3 to 1	2.5–10 mg	15–30 mg	3–4 h	UGT2B7	Glucuronides (M3G and M6G)	Hypotension, bronchospasm, pruritus, miosis, nausea, constipation, urinary retention, respiratory depression, biliary spasm, euphoria	
Morphine long acting	MS Contin, Kadian	n/a			15 mg	12 h				
Codeine		0.15	n/a	n/a	15–60 mg	4 h	CYP3A4, 2D6	Norcodeine (90%), morphine (10%), glucuronides	Like morphine	Pro-drug: heterogeneity in enzymes may cause it to be ineffective in some populations. It can cause fatal neonate respiratory depression
Semisynthetic										
Hydrocodone	Vicodin, Zohydro, Hysingla, Norco	1	n/a	n/a	2.5–10 mg	3–5 h	CYP3A4, 2D6	Norhydrocodone, hydromorphone	Like morphine	
Hydromorphone	Dilaudid	4	5 to 1	1–4 mg	2–8 mg	2–4 h	UGT1A3, 2B7	Glucuronides (HM3G)	Like morphine	Extensive liver metabolism, preferred in patients with renal disease

Oxycodone	Oxecta Roxicodone, Percocet	1.5	n/a	n/a	5–15 mg	3–5 h	CYP3A4, 2D6	Noroxycodone, oxymorphone	Like morphine	
Oxycodone long acting	Oxycontin	n/a	n/a	n/a	10 mg	12 h			Like morphine	
Oxymorphone	Opana	3	10 to 1	1–1.5 mg	10–20 mg	3–6 h	UGT2B7	6-HO-OM, OM3G	Like morphine	Contraindicated in patients with moderate-to-severe liver impairment
Oxymorphone long acting	Opana ER					12 h				Discontinued in the USA
Diacetylmorphine										Discontinued in the USA
Anilidopiperidines										
Meperidine	Demerol	0.1	1 to 1	50–150 mg	50–150 mg	3–5 h	CYP3A4, 2B6, 2C19	Normeperidine	Repetitive dosing can cause CNS hyperexcitability and seizures. Avoid in patients taking MAOI	Oral route least effective
Fentanyl	Duragesic	2.4 mcg/hr	n/a	50–150 mcg	n/a	2 h	CYP3A4	Norfentanyl	Like morphine	Available in transdermal system (iontophoretic and patch) and intranasal spray

(continued)

Table 6.1 (continued)

	Brand name	Morphine equivalents	PO:IV	Parental dose	Oral dose	Duration of action (h)	Enzyme	Metabolites	Side effects	Notes
Diphenylheptanes										
Methadone	Dolophine, Methadose	4–12*	1 to 1	2.5 mg	2.5 mg	4–8 h	CYP2B6	EDDP	Like morphine + QT prolongation	Useful in patients with morphine allergy, potential for QT prolongation. May need to increase dose or frequency in pregnant patients
Propoxyphene	–						CYP3A4	Norpropoxyphene		Discontinued in the USA
Diphenoxylate	Lomotil							Diphenoxine		Diarrhea treatment
Loperamide	Imodium, Diamode						CYP2C8, CYP3A4			Diarrhea treatment
LAAM										Discontinued in the USA
Oripavine derivatives (thebaine metabolite)										
Buprenorphine	Subutex, Suprenex	30		300 mcg	2–24 mg sublingual	Varies (acute or chronic pain, addiction)	CYP3A4	Norbuprenorphine, glucuronides	Partial agonist: may precipitate withdrawal in patients taking other opioids	Sublingual administration for chronic pain and opioid use disorder
Morphanin derivatives										
Butorphanol	Stadol	7	n/a	0.5–2 mg	n/a	4 h	CYP3A4		Like morphine	Partial agonist
Nalbuphine	Nubain	1	n/a	10 mg	n/a	4–6 h	CYP3A4, CYP2C19		Like morphine	Partial agonist
Levorphanol	Levo-Dromoran	11	n/a	n/a	1–2 mg	6–10 h	UGT2B7		Like morphine	Less drug-drug interaction

UGT 2B7- UDP glucuronyltransferase; UGT1A3=UDP glucuronosyltransferase 1-3; UGT 2B6=UDP glucuronosyltransferases 2 family; CYP=cytochrome p450 lar route for the administration of analgesics for the management of postoperative pain. Many of the opioids available including morphine and hydromorphone can be administered in a subcutaneous route as well. Intermittent subcutaneous opioid administration has the advantage of slow rate of absorption providing less side effects like nausea or sedation. Subcutaneous administration is more commonly used in palliative care and cancer pain management. Its role in postoperative needs to be determined.

IV opioid administration is the most rapid and effective means of delivery of opioids. IV patient-controlled analgesia (PCA) is recommended when parenteral administration of analgesics is necessary in hospitalized patients (e.g., ileus, aspiration risk, surgical procedures that preclude oral intake). PCA is recommended for the patients that will require analgesia for more than a few hours and patients that have adequate cognitive function and intellectual ability to understand the device and use it safely [18].

Sublingual administration may be a useful route when swallowing is impaired. This route allows opioids to enter systemic circulation directly via transmucosal absorption. Suppository forms of many opioids provide other option for patient that cannot tolerate oral medications.

Dose and Formulation Pain is usually continuous immediately after surgery and often requires around-the-clock dosing during the first 24 h [18]. Short-acting opioids are often preferred over long-acting because of the need to titrate doses and the lack of evidence suggesting that long-acting oral opioids are superior to short-acting ones in the immediate postoperative period. Short-acting opioid formulations with a quick onset of action are beneficial in achieving rapid analgesia, and the dose can be easily adjusted to address fluctuating pain levels. Long-acting opioids like sustained-release morphine and methadone have a role in the post-operative period, especially once the acute pain has been stabilized, meaning that the opioid tolerance has been established, and the pain is likely to remain severe and continuous for several days. The longer action of these agents results in less fluctuation in analgesic effect, reduced peak levels, and, therefore, fewer side effects.

Opioids can be prescribed on an as-needed or fixed-dose schedule. When the acute postsurgical pain that is severe and continuous fixed-dose schedule is recommended. In patients with severe and continuous pain, using an as-needed (PRN) dose schedule can make the patient feel dependent because they need to ask staff for pain medications. The patient can become excessively preoccupied about receiving pain medications and cause strong emotional reactions in both patient and staff. Scheduled dosing is preferred over PRN administration in patients with substance use disorders (to reduce the reinforcement of drug seeking behavior) and in patients with cognitive impairment, whose ability to participate in the decision about when to use PRN medications may be compromised. The as-needed schedule is recommended when the pain is intermittent and can be predicted, for example, when a patient is undergoing debridement of an ulcer or management of a wound.

Another scheduling method known as reverse PRN involves offering the medication in a scheduled basis but also allowing the patient to accept, refuse, or delay the dose [10].

Monitoring Clinicians need to monitor sedation and respiratory status during the initial hours after surgery. Patients should be assessed for alertness, hypoventilation, or hypoxia, especially those with sleep apnea or using other CNS depressant medications. If the patient is too sedated, delirious, or hypoxic, the opioid dose should be decreased. Rarely, a patient might require opioid antagonist therapy to reverse respiratory depression or oversedation [18].

Alternatively, in some cases the patient will continue to report pain despite use of analgesics. It is important to assess for medication interactions that might affect the metabolism of the analgesic. For instance, codeine is a prodrug and needs to be converted into its active form by the CYP 450 2D6 enzyme. Approximately 7% of the population are considered poor metabolizers, with limited activity of this enzyme [10]. Several medications like paroxetine or fluoxetine inhibit the CYP 2D6 enzyme. Such patients would receive suboptimal pain control on routine doses of codeine.

Tapering Opioids When opioids are taken on a regular basis, physiological dependence is likely to develop. This process usually requires 3 weeks or more of consistent opioid use [10]. In the physiologically dependent patient, sudden discontinuation leads to uncomfortable withdrawal symptoms. Withdrawal from agents with shorter half-lives will be more rapid and severe. Withdrawal symptoms include abdominal pain, diarrhea, muscle aching, lacrimation, and rhinorrhea. To prevent these symptoms, opioids should be tapered slowly, cutting down the dose by 20–25% per day as tolerated. In chronic opioid use, the taper should be slower.

Anti-inflammatories and Acetaminophen

Acetaminophen and NSAIDs are commonly included as a feature of multimodal analgesia for postoperative pain. Many studies suggest that the use of these medications in conjunction with opioids is associated with less postoperative pain and a lower opioid requirement than the use of opioids alone [18, 30, 31]. In fact, because acetaminophen and NSAIDs have different mechanisms of action, the combination of both might be more effective than either medication alone [32].

NSAIDs reduce inflammation and alleviate pain. They should be avoided in patients undergoing cardiovascular surgery because they are associated with increased risk of cardiovascular events including myocardial infarction and stroke. NSAIDs are also associated with gastrointestinal bleeding and renal dysfunction. Gastrointestinal risk is thought to be less with cyclooxygenase 2-selective NSAIDs like celecoxib; however, like other NSAIDs they compromise the glomerular filtration rate in patients at increased risk of kidney impairment and may promote a prothrombotic state, which is thought to explain the increased cardiovascular risk associated with their use [33]. The administration of celecoxib before surgery may reduce pain scores after surgery but should not be used in cardiovascular procedures [18]. Acetaminophen use is limited by its adverse effects on the liver. It should be used with caution in patients with chronic alcohol use or hepatic impairment. Pain management in patients with cirrhosis is challenging but can be achieved. Acetaminophen can be used at a reduced dose with cautious titration and careful monitoring.

Corticosteroids including dexamethasone and methylprednisolone are also important analgesics in the treatment of some acute pain syndromes due to their peripheral and central anti-inflammatory effects. Corticosteroids inhibit prostaglandin synthesis and decrease vascular permeability thus preventing edema. They are commonly used in neurosurgical procedures, as adjuvants in cancer pain [34] and during radiation therapy where spinal cord compression is present [10]. They are also used in the management of postoperative pain from tonsillectomy.

Antidepressants

The analgesic effects of tricyclic antidepressants like amitriptyline and nortriptyline have been attributed to their enhancement of monoamine pathways in the CNS. Their use may be limited due to anticholinergic side effects. Similarly, serotonin norepinephrine reuptake inhibitors (SNRIs) like duloxetine can be used for pain management, but their use in the immediate postoperative period is uncommon due to their lack of acute efficacy. In addition, these agents can interact pharmacokinetically with other analgesics and may also increase risk of bleeding. It is also notable that anxiety often worsens in the short term when starting an SNRI. These agents are recommended for the subacute period of pain management and in the transition to chronic pain.

Gabapentin, Pregabalin, and Other Anticonvulsants

Gabapentin and pregabalin are ligands of the alpha-2 delta receptor, thereby modulating voltage-gated calcium channels. They are associated with reduced opioid requirement after surgical procedures and lower pain scores [35, 36]. Both medications can be administered pre- or postoperatively. There is no consensus about optimal dosing, but higher doses are generally more effective [18]. These medications are recommended as part of the multimodal approach to pain management postoperatively, especially in opioid-dependent patients. Gabapentin bioavailability is dose-dependent because its absorption in the duodenum is saturable; higher individual doses—typically above 900 mg—are absorbed unreliably. However, the absorption of pregabalin is not dose-dependent. Both gabapentin and pregabalin are exclusively excreted by the kidneys, which makes them ideal adjuncts in patients with hepatic impairment but increasingly hazardous as kidney function declines.

Carbamazepine as a neuromodulating anticonvulsant drug has a role in the management of pain, especially in trigeminal neuralgia, post-stroke pain, fibromyalgia, and other neuropathic and centralized pain processes [37].

Ketamine

Intravenous ketamine has been evaluated as part of the comprehensive management of postoperative pain and is effective in decreasing pain scores and pain medication requirement after surgery. It is also associated with reduction of nausea and vomiting after surgery [38]. Ketamine for postoperative pain may be administered before or after incision or in the postoperative period. It is usually given as an adjunct to opioids. Experts recommend ketamine be reserved for major surgeries, highly opioid-dependent patients, or patients that experience opioid-related side effects [18]. Ketamine has been shown to benefit patients who require large amounts of opioid medications or exhibit some degree of opioid tolerance [39]. Clinicians should also be familiar with side effects of ketamine including nightmares, hallucinations, or confusion.

Antipsychotics

Antipsychotic medications have a role as adjuvant agents in the management of pain syndromes. Small sample size studies on the utilization of antipsychotic medications for pain management have yielded mixed results, and they failed to state clearly the difference between sedation and analgesia in their outcome measures. The risk of extrapyramidal symptoms and sedation limit their use. Neuroleptanalgesia, a state of altered awareness and analgesia produced by a combination of taking an opioid analgesic and an antipsychotic, may negatively influence disease course and total mortality in patients with unstable angina [40]. However, studies have shown benefits of antipsychotics reducing pain intensity in acute and chronic pain. The mechanism by how antipsychotics work to relieve pain is still under debate and may differ among agents. Risperidone, for instance, has a potent antinociceptive effect in vitro in animal models of pain [40]. The evaluation of risperidone with selective opioid antagonists has revealed the involvement of μ1-, μ2-, and kappa1-opioid receptors, each of which is involved in pain perception [40]. Atypical antipsychotics are generally preferred to typicals, especially as adjuncts for pain management, because they are relatively better tolerated and are more likely to have analgesic activity [40].

Topical Treatment

Capsaicin is a topically applied nonnarcotic that acts on the peripheral receptor TRPV1, which is present on C fiber terminals and downregulated in inflammatory states. It is typically applied as a cream and usually combined with NSAIDS to relieve pain. It may be used for postsurgical complications like neuromas or neuropathic pain [6].

Fentanyl iontophoretic transdermal system (ITS; IONSYS®) is a needle-free, preprogrammed drug-delivery system indicated for the management of acute postoperative pain in the hospital setting. This system delivers fentanyl through the skin by application of low-intensity electrical field. It provides equivalent analgesic efficacy to that of morphine PCA. Its convenience (i.e., preprogrammed) and ease of use (needle-free) offer potential advantages over alternatives [6, 41].

Non-pharmacological Interventions

Physical Treatment

Transcutaneous electrical nerve stimulation (TENS) can be used as an adjunct to other postoperative pain treatments [18]. TENS is administered by a portable device that delivers low-voltage electrical currents through the skin, which are thought to activate descending inhibitory pathways thereby activating opioid receptors, reducing central excitability, and ultimately causing analgesia [18]. Studies have shown that TENS can be helpful as an adjunct in treating moderate postoperative pain [42]. When administered with adequate intensity and frequency at the wound site, TENS significantly reduces analgesic consumption for postoperative pain, [43] with an apparent dose-dependent effect (i.e., sufficient intensity and frequency stimulus) [43].

Other physical interventions include massage, acupuncture, cold therapy, localized heat, warm insufflation, continuous passive motion, immobilization, or bracing. These interventions are safe, but evidence of their efficacy is broadly inconsistent [18].

Psychological Interventions

Multiple psychological interventions have been evaluated as adjunctive treatments in the postoperative setting. Muscle relaxation, guided imagery, hypnosis, and music therapy have been evaluated as part of multicomponent relaxation intervention. Such interventions can be provided by physicians, psychologists, nurses, or social workers but require specialized training. Most studies of these interventions have demonstrated positive effects on postoperative pain, analgesic use, and anxiety [18, 44] (see Table 6.2 for a representative selection of randomized clinical trials). Importantly, these interventions are noninvasive and associated with no more than a nominal risk of harm. They are particularly useful in older adults who are at risk of side effects from analgesics including oversedation and delirium with escalating doses of opioids.

Pain is not merely physical; it also involves a state of psychological distress or discomfort. High preoperative stress, anxiety, or pessimism predicts poor outcomes in measures ranging from speed of wound healing to duration of hospital stay. By contrast, psychological resilience and preparedness are associated with an enhanced capacity for pain control [9, 45]. Relaxation techniques and strategies like guided imagery are beneficial after surgery [46] (see Chap. 7 perioperative psychological interventions for detailed discussion).

Cognitive behavioral therapy (CBT) is an effective strategy in reducing pain and potentially associated dysfunction, but its use is typically restricted to managing chronic pain. CBT is a structured, problem-specific, and dynamic therapeutic approach that can help the patient develop coping mechanism to deal with pain. Additional CBT modules such as activity pacing or behavioral activation optimize functional activity.

Inadequate Pain Management

Barriers to adequate pain management extend beyond patient-related factors alone and include the individual prescriber as well. Some barriers include cultural attitudes about pain as being an inevitable part of surgery, implicit bias about pain thresholds in specific ethnic minorities [47], failure to address patient concerns about potential side effects or developing an addiction even with judicious analgesic use, prescriber fear that the patient will misuse analgesia, or perhaps even fear of disciplinary action due to inadequate medical training in pain management [10].

One of the most common causes of inadequate pain management is the underuse of opioid analgesia [10]. In addition to inadequate doses, opioids are often prescribed at time intervals that are excessive, leaving the patient vulnerable to pain between doses. Three key factors often explain suboptimal perioperative pain management—physiological dependence, opioid-induced hyperalgesia, and pseudoaddiction—as discussed below.

Physiological Dependence

When a psychoactive substance is taken consistently for an extended period, neuroadaptation to the substance occurs leading to physiological

Table 6.2 Selected randomized controlled trials of psychotherapy for postoperative pain management

Study	Surgery	Study size (n)	Psychotherapy	Duration/sessions	Timing	Outcomes	Results	Comments
Archer 2016	Lumbar spine	46	CBT-physical therapy	Six sessions	Preoperative	Pain and disability	Decrease in pain and in disability	CBPT provides meaningful improvement in pain and disability compared to education alone
Doering 2016	Cardiac	53	CBT	Eight sessions	Postoperative	Depressive symptoms, perceived control and pain	Increased in perceived control and decreased pain interference and severity	No effect found in sleep disturbance
Rolving 2016	Lumbar spinal fusion	90	CBT	Four 3-h group sessions	Preoperative	Back pain in first week, mobility, and analgesic use	No difference in back pain reported. Mobility and analgesic use better in CBT group	May reflect an improved ability to cope with pain
Forward 2015	Joint replacement	225	Structured touch and guided imagery	Four sessions, each 18–20 min	Postoperative	Pain and anxiety, use of pain medication	Reduction of pain and anxiety	No significant difference in opioid use Structured touch led to better outcomes
Rolving 2015	Lumbar spinal fusion	90	CBT	Preoperative one-time intervention	Preoperative	Change in Oswestry Disability Index from baseline, levels of catastrophizing, fear avoidance belief, work status, and back and leg pain	Intervention did not produce better outcomes at 1-year follow-up or in secondary outcomes	

(continued)

Table 6.2 (continued)

Study	Surgery	Study size (n)	Psychotherapy	Duration/sessions	Timing	Outcomes	Results	Comments
Wang 2014	Gynecological or lower limb orthopedic surgery	40	Music therapy + breathing exercise	30 min before procedure, during procedure, and two interventions after surgery	Preoperative Intraoperative Postoperative	Anxiety, postoperative pain, changes in heart rate variability, and sympathovagal tone 6 h after surgery	Decreased sympathovagal tone, anxiety scores, and postoperative pain	Population: elderly patients undergoing elective surgery
Binns 2011	Mastectomy for breast cancer	30	Music therapy	Unspecified perioperative music interventions	Preoperative Intraoperative Postoperative	Mean arterial pressure (MAP), heart rate, anxiety, and pain	Decrease in MAP and anxiety with less pain from the preoperative period to the time of discharge from the recovery room	
Gavin 2006	Lumbar and cervical spine	49	Relaxation training	Instruction on relaxation techniques	Preoperative	Pain score and opioid use in the first 48 h after surgery	Pain scores and opioid use higher in the relaxation group on postoperative day 1	Results don't support the use of relaxation training for reducing postoperative pain and opioid demand
Gilliss 1993	Cardiac	156	Psychoeducation + CBT	Variable	Postoperative	Mental distress, level of mobility	Greater self-efficacy expectations for mobility	Nursing intervention: slide/tape presentation and phone contact weekly for up to 8 weeks
Miller 1990	Cardiac	29	Deep breathing relaxation	One session	Preoperative	Blood pressure, heart rate, respiratory rate, report of pain	Decreased blood pressure, heart rate, respirator rate, and report of pain	No significant differences in analgesic use

CBT=Cognitive behavioral therapy

dependence [48]. Physiological dependence describes a biological need of a substance at a certain dose to maintain clinical stability. It may present as *tolerance*, which describes the adaptation that leads to reduced drug potency. A patient with tolerance will require escalating doses for the same clinical effect; else the same, consistent dose will provide a diminishing clinical effect [49]. If the substance is discontinued or tapered in a patient with physiological dependence, a clinical *withdrawal syndrome* typically occurs [50].

Although physiological dependence and addiction are distinct phenomena with unique neurophysiological mechanisms and psychosocial implications, healthcare professionals often view these conditions as synonymous. Such misperceptions can contribute to inadequate treatment of pain, especially when a patient's pain is severe [51].

Tolerance must also be differentiated from loss of pain control due to a new or advancing disease or inadequate treatment. The rate of development of tolerance varies, but patients who are exposed to continuous doses of opioids may develop tolerance in as few as 7 days [10]. Tolerance can lead to inadequate pain management; for these patients, it is often necessary to increase the opioid dose to achieve the previous level of pain relief.

Opioid-Induced Hyperalgesia

Opioid-induced hyperalgesia (OIH) is a phenomenon that explains the loss of opioid efficacy in some patients in the absence of disease progression. It is described as a state of nociceptive sensitization caused by exposure to opioids [39, 52, 53]. It usually occurs in patients on high-dose chronic opioid therapy—for example, patients on methadone maintenance for opioid use disorder or chronic pain. It can cause diffuse allodynia in addition to suboptimal pain management. Opioid-induced hyperalgesia has also been described in patients that receive high intraoperative doses of opioids, which can cause a small but significant increase in acute pain after surgery [52, 54].

The treatment of this condition can be challenging because it often involves tapering off opioids in a patient who is experiencing pain and the patient is likely experience withdrawal symptoms. Some recommendations include (1) tapering off opioids while managing the withdrawal symptoms and adding non-opioids agents along with behavioral strategies as part of a broader multi-modal approach, (2) switching to another opioid agent, (3) utilizing NMDA-receptor antagonists like ketamine, (4) introducing opioids with unique characteristics like methadone, which has incomplete cross-tolerance with other opioids and has NMDA antagonism, or buprenorphine, which is more effective at managing hyperalgesia due to its known kappa and delta receptor antagonism. Spinal dynorphin, a kappa receptor agonist, increases during opioid administration, thus contributing to OIH [39].

Pseudoaddiction

Pseudoaddiction is an iatrogenic syndrome that occurs when a patient with genuine pain is given opioids of inadequate potency or ordered with inappropriately long-dosing interval [55]. The patient will request higher doses, more frequent administration of medication, and may eventually become distressed and angry or even be behaviorally disruptive. These responses to the clinician are not uncommonly misinterpreted as an addiction, but the patient, by exhibiting a change in emotions or behavior, may simply be trying to impress on the clinician their unmet need for adequate pain relief.

Special Populations

Several special situations offer challenges to providing pain management in the postoperative setting. Patients with cognitive impairment, those with intellectual or other developmental disability, and the geriatric and the pediatric population are more likely to receive inadequate pain management. Pain scales should be developmentally appropriate and understood by the patient. In these special populations, accurate pain assessment and management should also involve family and caregivers. Finally, patients with substance use disorders require close attention and consideration for their unique postoperative pain care needs. This section reviews the complexities of treating postoperative pain in the geriatric population and the patient with addiction.

Geriatric Population

Analgesics should typically be initiated at lower doses in this population especially in those with hepatic or renal insufficiency because of alterations in drug metabolism and effective half-life [10]. Clinicians should monitor closely for confusion or intoxication, sedation, and respiratory depression when using opioids. Additionally, older adults tend to have multiple medical comorbidities and, as such, are often prescribed multiple medications. The clinician should be vigilant for medication interaction and adverse effects. For instance, opioids that are known to prolong QTc like methadone should be used cautiously in patients receiving other QTc-prolonging agents or in patients who are at risk of potassium or magnesium abnormalities. In addition, potent opioids are associated with falls [56] due to their effects on vision, cognition, motor coordination, and reaction time.

Patients with Addiction

Addiction (synonymously, a substance use disorder) is characterized by a maladaptive pattern of behavior leading to functional impairment in addition to the neurophysiological adaptation that occur with the prolonged use of a psychoactive substance. That is, addiction involves loss of control over drug use, compulsive use despite harm, and increased time spent obtaining, using or recovering from the drug, all of which cumulatively leads to functional impairment including failure to meet major responsibilities at work, school, or home. In the clinical setting, the clinician can suspect addiction when there are irregularities in a patient's story, evidence of physical complications related to a substance like alcoholic cirrhosis, unexpected findings in toxicology screens, or concerning patterns of prescriptions on a state prescription monitoring program website. Other findings suggestive of addictions are inconsistencies with follow-up appointments, repeatedly consuming the prescription earlier than prescribed, reports of losing medications, or use of opioids for euphoria or sedation.

There are multiple misconceptions about the understanding of pain in the patient with addiction. Many clinicians may assume that the patient will invariably use medication to "get high," that pain medications are not going to be effective, or, for the methadone-maintained patient, that continuation on preoperative dose of methadone should be sufficient to treat postoperative pain [57]. Pain and addiction should be differentiated to the extent possible and treated separately [10]. Patients with opioid use disorder (OUD) should be expected to require higher doses than the average patient for adequate postoperative pain relief due to opioid tolerance. In patients on methadone maintenance for OUD, methadone should be continued either as once daily or split daily dosing. In addition to this, the use of a different opioid should be used for the treatment of acute pain [10].

Buprenorphine is a high-affinity mu opioid partial agonist commonly used to treat OUD. Because of its pharmacodynamics, it occupies the opioid receptor with great affinity, often displacing other opioids. When administered to a patient already on a full mu agonist, it induces withdrawal symptoms and can worsen of pain. However, when a patient on a scheduled regimen including buprenorphine is given a full mu opioid agonist such as morphine, buprenorphine limits the effect of the other opioid. As such, buprenorphine should be held 24 h before surgery, and a shorter-acting opioid agonist should be started to prevent withdrawal. The treatment of acute pain should continue in the postoperative period. Buprenorphine induction can be performed again for the treatment of OUD when the need for acute pain treatment is completed.

Inadequate pain treatment in patients with OUD may lead to behavioral abnormalities, opposition to care, and requests to leave the hospital against medical advice and, in some cases, to relapse to opioid use after surgery. Patients with addiction need to be monitored for unexpected changes in mental status. If a patient develops acute change in mentation, the patient needs to be evaluated, and if appropriate a urine toxicology should be obtained.

Patients with Difficult Personality Traits

Psychological distress, pain severity, and underlying psychological predisposition are related in interesting ways. Levels of psychological distress are related to both the patients' personality and the characteristics of their illness or pain process. Patients with high levels of neuroticism tend to have higher levels of psychological distress than patients who score low on this trait [58]. Similarly, patients who have more severe pain and functional impairment also tend to report higher levels of psychological distress [58]. Postoperative pain, affect, and analgesic requirements are also influenced by psychological variables. For instance, high levels of catastrophizing (the cognitive distortion where a person imagines the worst outcomes) in postsurgical patients are associated with a heightened pain experience [59] and appear to contribute to the development of chronic pain [60]. Another trait that appears to be important is pain acceptance, which is often inversely related to harm avoidance. Pain acceptance generally facilitates mental well-being and is related to better functional outcomes for chronic pain patients [61].

Transitioning to the Outpatient Setting

Education and Counseling

Patients and families should be counseled about taking analgesic medications safely to ensure functional recovery. Appropriate monitoring should be arranged for patients with history of addiction and for those who are concurrently prescribed sedatives like benzodiazepines. It is also imperative to educate patients about the potential effect of opioids on one's ability to drive safely and the potential for other CNS depressants like alcohol to augment the sedative effect of opioids. Treatment with analgesics in the postoperative setting should also entail discussions about the goals of pain therapy, emphasizing functional recovery to pre-surgical activities. Part of this discussion will involve a clear explanation of anticipated opioid dose reduction and eventual discontinuation. For patients who have developed physiological dependence due to extended opioid use, dose reductions of 20–25% per day are common [18]. Patients also should be informed about the need to secure their medications to avoid diversion or potential theft. Patients should be aware that it is their responsibility to notify the clinician if the location, quality, or severity of pain changes or worsens, which could suggest complications.

Persistent Postsurgical Pain

Pain that persists after the surgical wound has healed is known as persistent postsurgical pain, and it can last for more than 6 months after surgery [5]. This type of long-term pain is a common sequela of thoracotomy, and when this occurs it is typically described as an aching or burning pain along the thoracotomy scar persisting for at least 2 months. Pain persistence represents a transition from acute to chronic pain. The strongest predictor of long-term postoperative pain is early postoperative pain [62], which has led some to hypothesize that aggressive management of early postoperative pain may reduce the likelihood of transitioning to a long-term pain syndrome. Patients with preoperative opioid use will typically take longer for postoperative pain to remit than patients without preoperative opioid use [63]. Further, patients taking opioids before surgery are more likely to experience relatively poor pain control and even cognitive dysfunction postoperatively [63]. Preoperative chronic pain, anxiety, and neuropathic pain are associated with postoperative pain intensity [64].

Transitioning to Chronic Opioid Use

According to some estimates, nearly 50% of patients who were not on opioids preoperatively are discharged from the hospital with an opioid prescription after surgery [65]. Of these, 3% of patients continued to receive opioids 90 days after the surgical procedure, which represents a public health concern. Younger age, lower household income, and number of medical comorbidities especially including diabetes and heart failure are among the risk factors associated with prolonged postoperative use of opioids in patients not on opioids preoperatively [65]. Risk factors specifically associated with chronic opioid prescribing for pain include male gender, advanced age, and history of substance use disorder [66]. In fact, preoperative addiction may be missed at the time of the surgery but be identified retrospectively as concerns emerge in the months following surgery. Chronic pain is a known adverse outcome of surgery and is costly in terms of suffering, morbidity, and disability [67].

The Centers for Disease Control and Prevention (CDC) created guidelines for prescribing opioids for chronic pain in 2016 [68]. The evidence for prescribing opioids for chronic pain is very limited; therefore, the CDC recommends both non-pharmacological and non-opioid pharmacological interventions. When opioids are initiated, the clinician should define the treatment goals clearly with emphasis on recovery or maintenance of functional status. The CDC encourages clinicians to prescribe the lowest effective dose, avoiding doses above 90-mg morphine equivalents per day. Clinicians should discontinue opioid therapy if the benefits do not outweigh the risks, and prescriptions are best limited to 7 days at a time. Additionally, clinicians are recommended against prescribing a benzodiazepine concurrently with an opioid to avoid complications. Clinicians are urged to monitor urine toxicology regularly and to review their state's prescription drug monitoring program.

Regulatory Measures

Prescribed opioids can lead to misuse, addiction, diversion, and either willful or unintentional overdose. Death related to prescription opioids increased fourfold from 1999 to 2013 [69]. The National Center for Health Statistics and the CDC reported that the rate of drug overdose deaths have continued to increase since 2013. In 2015, the rate of drug overdose deaths was 2.5 times the rate in 1999. More than two thirds of patients reported unused prescription opioids following surgery [70]. These medications can be diverted for nonmedical use.

Although federal regulations limit the distribution of controlled substances, many states have passed laws to address the over-prescribing of opioids and prevent complications of opioid use, and law enforcement has ramped up to keep pace with public health concerns [71]. As of late 2017, state prescription monitoring programs are established in every state except Missouri (*n.b.*, which is currently working on launching this program). Early evidence has found that these statewide databases are associated with a reduction in drug abuse/misuse over time [72]. As part of comprehensive state opioid legislative initiatives, many states have delineated opioid prescribing limits for acute pain in the outpatient setting, limiting first-time prescription to 7 days. Additionally, many states have increased access to opioid antagonists such as naloxone among police officers to reverse opioid overdoses in the field. These measures are intended to curb the potential complications of opioid misuse and abuse. Clinicians should be informed about state-specific regulations to improve prescribing practices and to ensure safe, effective pharmacotherapy. Clinician education is a primary means of combating the common fear of disciplinary action and safeguarding best clinical practice.

Conclusions

Pain management is an essential component of the perioperative process. Effective pain management facilitates recovery after surgery and ensures an expedient return to preoperative levels of functioning. Acute postoperative pain is all but universal. The assessment and management of pain should begin before surgery and include education about the goals of pain treatment and a candid discussion about pain expectation. It is important to craft an individualized multimodal pain management plan that includes both non-pharmacological and pharmacological interventions for optimal outcomes. Opioid analgesia is the mainstay in treating acute postoperative pain. Nevertheless, evidence strongly suggests that the combination of opioid and non-opioid pharmacology, along with non-pharmacological interventions, yields the best outcomes including lower pain scores and lower total dose of analgesics. Systemic, topical, physical, and psychological interventions are expected to have synergistic effects on pain control. Flexibility of dose, dose interval, and route of administration is often necessary to ensure adequate pain management. Monitoring for analgesic side effects is critical to prevent oversedation and respiratory depression.

Despite significant efforts to provide best pain management, a patient may yet report severe distress and disability related to pain. When this occurs, the clinician should explore whether the patient may be receiving inadequate doses of analgesics, physiological dependence has developed, or opioids may be paradoxically causing hyperalgesia. Non-pharmacological interventions should be pursued assertively as well. Special populations including older adults, children, cognitively or developmentally vulnerable patients, and those with addiction call for especially careful attention. A comprehensive pain management plan should also include instructions and education about aftercare management that incorporates safe, effective analgesia with the goal of rapid functional recovery.

Take-Home Points

- Postoperative pain, when not managed well, can lead to delayed functional recovery and increased risk of postsurgical complications including poor wound healing and even cardiovascular events.
- Preoperative education about postoperative pain management, expectations, and available treatments has shown to reduce postoperative anxiety, opioid requirement, sedative demands, and length of stay after surgery.
- Multimodal analgesia is a well-established treatment option recommended for management of postoperative pain. It involves both pharmacological (opioid and non-opioid) and non-pharmacological treatments (behavioral and physical measures).
- During the postoperative period, a patient can become excessively preoccupied about receiving pain medications, and this may elicit strong emotional reactions in both patient and staff. Pain is not merely physical; it also involves a state of psychological distress. Anxiety and pessimism predict poor outcomes in measures ranging from speed of wound healing to duration of hospital stay.
- The monitoring of pain should include the identification of surgical or medical complications in the postoperative period, verification of the dose and scheduling of the pain medications, and also the identification of factors that can interfere with adequate pain management including physiological dependence or the existence of a substance use disorder.

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7 Perioperative Psychological Interventions

Dwain C. Fehon and Amelia Swanson

Introduction

Surgery is often viewed as a stressful and potentially traumatic emotional experience given the physical impact on the body and the potential for painful recovery and protracted rehabilitation. Even "minor" surgery may conjure fear and other strong emotional reactions [1]. The fear of pain, disfigurement, loss of function, loss of autonomy, and the uncertainty associated with physical recovery contribute to the stress many patients feel throughout the perisurgical period. Indeed, surgical complications when they occur have been found to be a significant and long-term predictor of a patient's postoperative psychosocial adjustment [2]. Despite these concerns, most patients cope reasonably well before and after surgery and require little more than standard supportive care to facilitate physical and emotional recovery. Nevertheless, pre- and postoperative depression, anxiety, pain, and delirium commonly accompany surgery and can have a significant impact on postsurgical outcomes during both the acute and rehabilitative phases of recovery.

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Researchers and clinicians have become increasingly interested in understanding how people cope with and adapt to physical illness and injury. Considerable work has been undertaken to understand the factors which contribute to an individual's risk for unfavorable emotional outcome following surgery. Likewise, considerable attention has been placed on understanding the factors that facilitate favorable outcomes, such as adaptive coping, benefit finding, and personal growth.

For individuals facing the potential trauma of a major surgery, several evidence-based psychotherapeutic approaches exist to treat adverse emotional reactions and to enhance coping and adjustment both before and after surgery. This chapter will focus on common pre- and postsurgical mental health concerns associated with major surgery, dominant conceptual models related to stress and coping, and common evidence-based psychotherapeutic approaches to enhance coping before and after major surgery.

Pre- and Postsurgical Mental Health

The circumstances that led to major surgery often have a significant impact on the way the surgery is anticipated and emotionally experienced. The extent to which an individual can plan, prepare, and view the surgery as helpful generally facilitates the individual's ability to cope with the

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surgical event. Unplanned or emergency surgeries for life-threatening conditions and surgeries that may leave the individual disabled or disfigured have a greater risk for adverse emotional adjustment. Likewise, protective factors such emotional health, resilience, the availability of social supports, adequate finances, and the availability of appropriate ongoing healthcare services can facilitate adaptive recovery.

Several premorbid and presurgical psychosocial factors are associated with postsurgical psychological adjustment. The patient's age, personality, premorbid psychiatric and behavioral health history, the reason for surgery, the availability of social support, and financial/vocational variables are all seen as significant predictors of psychological outcome following surgery. Older age, female gender, a history of anxiety, depression, PTSD, and substance use (smoking and alcohol and drug use) are associated with an increased risk of perisurgical emotional distress and postoperative complications [3]. Likewise, for those who experience chronic postsurgical pain, which occurs in 10–30% of all surgical patients, several factors including preoperative distress, a history of depression and anxiety, and specific health-related cognitions such as catastrophic thinking have been found to predict poorer emotional adjustment and lower quality of life [4].

Depression, traumatic stress, pain, and altered cognitive states, such as delirium, are relatively common and potentially significant complications that can affect surgical outcome and an individual's subsequent adjustment and adaptation after surgery. A brief description of these select perisurgical complications is given here:

Depression

Major depression is present in nearly 7% of all adults in the United States and is defined by a period of either depressed mood or loss of interest or pleasure, with at least four other symptoms that reflect a change in functioning, such as problems with sleep, energy, appetite, concentration, as well as excessive guilt or suicidal ideation for 2 weeks or longer and sufficiently severe enough to impair usual functioning [5]. Despite its incidence, depression remains a difficult topic for many people to discuss, and patients often minimize or underreport their symptoms to healthcare providers. Likewise, most clinicians do not thoroughly assess for symptoms of depression prior to or after surgery even though depression increases the risk of postsurgical infection, and depression is a potential predictor of postsurgical cognitive impairment (i.e., delirium) and postsurgical pain [6]. Indeed, the incidence of postoperative infections following coronary artery bypass graft (CABG) surgery [7], left ventricular assist device (LVAD) placement [8], and total knee replacement [9] is higher among patients with depression.

Depression is also a significant risk factor for morbidity and mortality following surgery. The association between depression and mortality is especially strong in the setting of cardiac and orthopedic surgery. The prevalence of depression following CABG surgery can be as high as 30–40%, and preoperative depression increases the risk of postoperative delirium, rehospitalization, and postoperative cardiac events such as arrhythmia and angina [10, 11]. Similarly, for patients who undergo common orthopedic surgeries such as spinal, rotator cuff repair, joint replacement surgery, sports-related surgery, and hand and upper extremity surgery, presurgical depression and poor emotional health (i.e., low mental health composite score on the Medical Outcome Study Short Form-36 [SF-36]) are associated with poorer functional outcome, lower postoperative quality of life, and reduced patient satisfaction [12].

Stress-Related Symptom Disorder

Circumstances leading up to and including surgery itself may be significant enough to engender post-traumatic stress symptoms (PTSS) in as many as 8–51% of patients depending on the nature of the illness/injury, type of surgery, and individual characteristics of the patient [13]. PTSS is viewed as a partial or subthreshold form of post-traumatic stress disorder (PTSD), which according to the *Diagnostic and Statistical Manual, Fifth Edition* [5], is characterized by the presence of intrusive symptoms (such as recurrent memories), avoidance, negative alterations in cognition or mood, and alterations in arousal for greater than 1-month duration and to a level that results in impaired daily functioning in response to or following a life-threatening event. Patients with PTSS and PTSD tend to have poorer outcome (greater risk of mortality, more frequent rehospitalizations, poorer health-related quality of life), due in large part to patients' difficulty engaging in good self-care activities and adhering to recommended postsurgical treatments that may exacerbate or trigger PTSD symptoms [14–18].

Specific sociodemographic and illness/trauma-related factors that prompt the need for surgery can have a significant impact on the development of PTSD symptoms [16]. For instance, individual sociodemographic characteristics of the patient such as socioeconomic status [13], female gender [19, 20], younger age [21], previous psychiatric history [13], anxiety sensitivity, and coping style vis-à-vis catastrophic thinking, avoidance coping, and ruminative thinking [22–24] have been found to predict the development of PTSD after surgery.

The type, severity, and onset of illness/injury can also predict the development of postsurgical PTSD symptoms. Patients with advanced cancer who undergo surgery have a greater risk of developing PTSD symptoms than patients with less advanced cancers [13, 25]. Likewise, surgeries for conditions with sudden/traumatic onset are more likely to be associated with more severe and persistent symptoms of PTSD than are surgeries for chronic conditions. One possible reason for this is that patients who undergo surgery for a less advanced or nonfatal chronic illness have time to prepare and may experience some degree of control and hope for improvement prior to surgery. In contrast, patients who undergo surgery due to a traumatic injury or due to a life-threatening illness such as an advanced cancer either have no time to prepare (as in the case of a traumatic injury) or may be faced with intense feelings of uncertainty and loss associated with a life-threatening diagnosis itself.

Additional factors related to intra- and post-surgical events have also been found to be associated with the risk for developing PTSD-related symptoms. For instance, surgeries where the individual becomes conscious and aware [26, 27] or is administered certain medications such as stress hormones (i.e., norepinephrine) are at increased risk for developing symptoms of PTSD [28]. Likewise, patients who have traumatic memories of postsurgical ICU admissions [20] are at increased risk for developing symptoms of PTSD as well.

Pain

Pain is a common and expected outcome following most types of surgery. Indeed, three out of four adult surgical patients report moderate to severe pain after surgery. Certain types of pain are particularly common such as abdominal cramping, muscle spasms, and nerve pain. In most cases, pain can be well managed and is temporary. However, when pain worsens and becomes more difficult to treat, the risk of adverse emotional reactions increases.

Up to one third of patients undergoing common surgical procedures report persistent or intermittent pain of varying intensity 1 year postoperatively [29]. Persistent pain is difficult to treat and is costly because it is often associated with increased healthcare utilization, reduced quality of life, and decreased economic productivity [4].

Uncontrolled or poorly controlled pain can result in extreme emotional distress, which often results in a worsening of both conditions. In some cases, uncontrolled pain can be traumatic and precipitate states of hopelessness, helplessness, demoralization, and depression. Unremitting pain is associated with an increased risk for suicidal behavior as a means to end one's suffering [30]. Persistent pain may also lead to avoidance behaviors (such as a reluctance to participate in physical activity or physical therapy for fear of exacerbating the pain) or a tendency to catastrophize thus worsening one's perception of the pain. The link between depression and pain is an important postoperative consideration, as depression prior to surgery has also been found to be significantly associated with postoperative pain measurements and analgesic requirements [31, 32].

Another important consideration involves the link between medical pain management practices and the risk of opioid abuse or dependence. Opioid dependence is a well-recognized potential adverse event that can develop even in opioid-naive patients [33]. Indeed, the overwhelming majority of opioid-dependent patients began their addiction with prescription medication, primarily for chronic pain which can develop in 10–50% of surgical patients [34]. Although they are an important component of postoperative pain management, opioids have become a major topic of debate given the epidemic misuse and abuse of prescription pain medications within the United States. As a consequence, to reduce the risk of opioid misuse, many states as well as the Centers for Disease Control and Prevention have issued opioid prescribing guidelines for chronic pain [35]. Within the postsurgical setting, vigilant monitoring is required to prevent both overdosing and underdosing of pain medication. Undertreatment of pain not only results in unnecessary pain and suffering but is also associated with a number of behaviors such as "clock watching," agitation, anxiety, and depression [33, 36].

Delirium

Delirium is often a highly stressful and confusing event for patients and family members alike. Delirium, defined as an acute and fluctuating disturbance of consciousness secondary to an acute medical condition [5], is a common and often distressing occurrence affecting between 10% and 24% of the general adult medicine population, and many as 37–46% of the general surgical population, with rates climbing to as high as 87% in the postoperative ICU setting [37]. The diagnosis of delirium is associated with poor medical outcome [38, 39] and increased healthcare costs [40], and its timely diagnosis and treatment are crucial to prevent severe and lasting complications [41]. Delirium during hospitalization doubles a patient's risk of post-discharge institutionalization and death and increases the risk of dementia tenfold [39]. Likewise, in-hospital delirium is associated with doubled 1-year medical costs largely due to delirium's association with other postoperative complications such as falls, pressure ulcers, urinary tract infections, and respiratory difficulties [40]. Postoperative delirium is also associated with increased risk for sustained decline of cognitive and functional status 1 year after surgery in the elderly [41–42] .

Accurate assessment and understanding of postoperative delirium is essential prior to initiating any bedside psychological intervention. Likewise, providers of psychological services need to be aware of subtle signs of delirium that may arise, as a consequence of medication, infection, or metabolic factors, during the course of psychological therapy.

Standards for Providing Psychological Interventions Within Medical Settings

Professional guidelines, federal and state laws, standards of accrediting bodies (e.g., Joint Commission), and institutional bylaws govern the rules and regulations by which healthcare providers may practice and engage in services of a psychological nature. A wide range of psychological and behavioral principles are routinely integrated within nursing and medical practice to enhance physical functioning and emotional adjustment, and specific evidence-based psychological interventions have been developed for behavioral health providers (e.g., psychiatrists, psychologists, and clinical social workers) who provide clinical care within medical settings. Professional standards for psychological consultation and intervention are well-established for behavioral health providers within clinical healthcare settings.

The American Psychological Association has published guidelines for psychological practice in healthcare delivery systems [43] and recognizes clinical health psychology and rehabilitation psychology as two defined specialty areas of psychological practice that require advanced knowledge and skills acquired at the doctoral level. Psychologists trained within these specialties may choose to achieve board-certified status through the American Board of Professional Psychology.

Clinical health psychologists are trained to apply scientific knowledge of the interrelationships among behavioral, emotional, cognitive, social, and biological components in health and disease to the promotion and maintenance of health; the prevention, treatment, and rehabilitation of illness and disability; and the improvement of the healthcare system [44]. Clinical health psychology (also known as behavioral medicine and medical psychology) lies at the juncture of physical and emotional illness, and it deals with understanding and treating psychological conditions in this context [44].

Rehabilitation psychology is the study and application of psychological principles on behalf of persons who have disability due to injury or illness. Rehabilitation psychologists, often within multidisciplinary teams, assess and treat cognitive, emotional, and functional difficulties and help people overcome barriers to participation in life activities. Rehabilitation psychologists are involved in practice, research, and advocacy, with the broad goal of fostering independence and opportunity for people with disabilities [45].

The National Association of Social Workers has published standards for social worker practice in healthcare settings [46]. Professional social workers provide services to individuals and families throughout the lifespan, addressing the full range of biopsychosocial–spiritual and environmental issues that affect well-being. Clinical social workers who are employed or contracted to provide mental or behavioral health services should use evidence-based treatment interventions with clients. These interventions may include cognitive–behavioral therapy, motivational interviewing, chronic disease self-management, psychoeducational services, brief intervention/brief therapy, and trauma-informed care, among others.

Within the postoperative setting, psychiatrists, clinical health psychologists, rehabilitation psychologists, and clinical social workers may be employed within psychiatric consultation–liaison services or as part of multidisciplinary specialty surgical teams to evaluate and treat patients before and after surgical intervention. Common reasons for psychological consultation and intervention include the evaluation and treatment of health-related depression, anxiety/panic, suicidal ideation, acute stress reactions to trauma, behavioral changes, psychosis, delirium, cognitive impairment, substance abuse, and decisional capacity.

Models of Psychological Adaptation Pertinent to Illness, Stress, and Coping

Models of psychological adaptation to illness, stress, and coping enable clinicians and researchers conceptualize the interrelated processes and dynamics of physical and emotional functioning. They provide clinicians a framework for engaging and educating patients and families about illness and effective adaptation, and they provide researchers a conceptual basis to develop and test novel treatments. Two leading models for conceptualizing health and coping are the biopsychosocial model [47] and the transactional model of stress and coping [48].

The biopsychosocial model, when first described by Engel at the University of Rochester [47], was a novel holistic approach toward understanding the relationship between the person, their physical and social environment, and their health. Unlike the traditional biomedical model, which attributed disease to biological factors alone, the biopsychosocial approach systematically considered the interaction between biological, psychological, and social factors to understand health, illness, and healthcare delivery. The model considered the interactive effects of disease, psychosocial stress, as well as personal and environmental factors that account for varying degrees of adaptation [49]. In this model, psychological factors can greatly affect chronic health conditions (such as persistent pain and depression), and psychosocial factors can predispose patients to medical illnesses (e.g., physical inactivity and poor diet can lead to obesity and hypertension in a person genetically predisposed to heart disease). The biopsychosocial approach has become the dominant model for understanding and conceptualizing physical and emotional health and well-being.

Perhaps one of the most widely referenced and researched models of coping is a cognitive model of stress and coping proposed by Lazarus and Folkman [48, 50]. This transactional model is based on an understanding of two basic processes: appraisal and coping. According to Folkman and Greer [51], *appraisal* describes an individual's evaluation of the personal significance of a given event and the adequacy of their resources for coping. *Coping* refers to the thoughts and behaviors a person uses to regulate distress (emotion-focused coping), manage the problems causing distress (problem-focused coping), and maintain positive well-being (meaning-based coping). *Appraisal* influences emotion and subsequent coping, while *coping* influences the outcome of the situation and the individual's subsequent appraisal of it.

In Folkman's model, the processes of *appraisal* and *coping* are influenced by characteristics of the person and the environment. Personal characteristics (such as an individual's temperament and personality) and environmental factors (such as noise and crowding within the individual's surroundings) influence (a) the appraisal of any given stressor, (b) the extent to which the situation can be controlled or changed, (c) the choice of appropriate coping strategy, and (d) the ability to use it effectively [51]. For example, psychoeducation about an involved surgical procedure may help with the appraisal of the procedure and thus decrease anxiety and provide the patient with a sense of control over certain aspects of the procedure. Likewise, psychotherapy can help with the development of effective emotion-focused coping strategies to manage the uncontrollable aspects of the stressor.

Lazarus and Folkman's model of stress, coping, and appraisal is consistent with tenets of cognitive behavioral therapy [52] and the view that thoughts, feelings, and behavior are all interconnected such that changes in one area result in changes in the others. Together, Engel's biopsychosocial model and Lazarus and Folkman's transactional model of stress and coping provide clinicians a functional approach to conceptualizing the complex interactions between the person, their environment, and their subsequent physical health and psychological well-being.

Evidence-Based Psychological Interventions Pertinent to Perisurgical Psychiatry

Several psychological interventions may help patients cope and adapt to the stresses of the perioperative setting. Specifically, there is a strong evidence base for psychological interventions to treat common issues that postsurgical patients face including pain, stress, depression, anxiety, and family conflict [53–56]. This section will highlight evidence-based interventions relevant to postsurgical patients and will be followed by a discussion of their application to common symptoms and problems encountered in the perisurgical setting.

Presurgical Screening and Preparation

Screening for mental health conditions, including substance abuse, and preparation for common postsurgical issues prior to surgery can identify concerns that should be addressed before the operation as well as improve postoperative outcomes. Researchers have found that presurgical levels of depression and anxiety predict postsurgical depression and anxiety [57–59]. Treatment of these disorders and symptoms prior to surgery could improve symptoms post-surgery and provide patients with needed skills to cope with stress post-surgery. Working with patients before surgery to ensure they have a realistic expectation of surgical recovery and to plan accordingly for their postsurgical psychological needs can improve coping in the perioperative setting [60]. This preparation may also include planning to rally social support to promote effective coping after surgery, with a focus on emotional and psychological support in addition to logistical and financial support.

Psychoeducation

Pre- and postsurgical patients routinely receive education about the surgery and recovery process. Despite this, patients may still have additional questions about what to expect with their recovery [60]. Psychoeducation focuses on providing education to patients about the impact of surgery on psychological issues such as anxiety, depression, and stress and how these psychological issues may interact with physical illness. Fully assessing for questions throughout the recovery process and addressing patients' concerns may help patients feel in control, reduce anxiety, and help patients anticipate the type of support they will need [61].

Stress Management

Stress management interventions encompass a wide range of approaches to help patients manage the psychological, emotional, and physical manifestations of stress [61]. Recovering from surgery, unexpected or planned, has many stressful components. Stress is often increased during the hospitalization and rehabilitation process due to interrupted sleep, unpredictable schedule, and acute physical symptoms. An individual's appraisal of these events and the choice of coping strategies they use will impact their subsequent physical and emotional response to the stressful events.

Relaxation Training

One important common component to stress management is relaxation training. The goal of relaxation training is to teach patients to become aware of their physical and mental tension and learn how to decrease their level of arousal and sympathetic nervous system activity. Relaxation training may include teaching *diaphragmatic breathing*, *progressive muscle relaxation*, and *guided imagery*. These skills can be taught in various settings and practiced with patients to enhance their effectiveness. There are also many websites and smartphone applications that include guided exercises to help patients practice diaphragmatic breathing and progressive muscle relaxation on their own. Some popular apps include Insight Timer, Calm, and Headspace (Boxes 7.1 and 7.2).

Consideration of the patient's physical status is important prior to teaching relaxation exercises. For example, care should be taken with these exercises with patients who have difficulty breathing as these patients may initially become more anxious when using diaphragmatic breathing as it further focuses their attention on their

Box 7.1 Stress management techniques

- Relaxation training
  - Diaphragmatic breathing
  - Progressive muscle relaxation
  - Guided imagery
  - Autogenic training
- Mindfulness
- Hypnosis
- Biofeedback

Box 7.2 A sampling of available smartphone apps and website

- 10% Happier
- Breathe2Relax
- Buddhify
- Calm
- CBT-I Coach
- HeadSpace
- Health Journeys
- Insight Timer
- Mindfulness Coach
- Simply Being
- The Mindfulness App
- Virtual Hope Box
- WebMD Pain Coach

breathing. Additionally, progressive muscle relaxation typically involves first tightening muscles prior to relaxing them and becoming more mentally aware of the difference between states of muscle tension and relaxation. It is often recommended that progressive muscle relaxation be avoided with patients who are experiencing pain. An alternative form of muscle relaxation is *autogenic training*, which involves mentally focusing on particular muscle groups and simply noticing the tension and learning to relax the muscles at will.

Guided imagery is stress management technique that involves focusing attention and imagining in detail a specific, usually relaxing, scene with a focus on the physical sensation of being in a different place. Participants are encouraged to visualize the details of a pleasant scene, usually while focusing on each of the five senses (i.e., imagining the sights, sounds, smells, tastes, and feel) associated with the scene while breathing regularly and allowing one's muscles to relax completely. Guided imagery has been found to increase comfort for cancer patients [62].

Mindfulness

Mindfulness has been described as "paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally" [63]. Some common aspects of mindfulness exercises are self-regulation of attention on a particular present focus such as breathing or a specific thought. Another common aspect of mindfulness is the development of a nonjudgmental standpoint with respect to own thoughts and experiences. This involves the ability to be aware of one's thoughts and accept them as they are, while gently letting them pass rather than becoming engaged or fixated on them. Mindfulness and meditation have been studied in several medical populations and found to have a moderate effect in reducing symptoms of anxiety, as well as a smaller effect in reducing symptoms of depression, pain, stress, and distress [60].

Several ways to teach mindfulness meditation have been described. They range from formal training programs that require weekly classes over months to brief, guided exercises that patients can practice on their own (e.g., free online resources and smartphones applications) (Box 7.2). *Mindfulness-based stress reduction* (MBSR) is a formal program through the Center for Mindfulness in Medicine, Health Care, and Society at the University of Massachusetts Medical School. The program consists of an 8-week course, with weekly classes and homework that takes place in a group setting. MBSR has been extensively researched in a number of medical populations and specifically has been found to be effective for patients with chronic pain [53], cancer [64], and hypertension [65]. The practice of mindfulness has been incorporated into other evidence-based treatments such as dialectical behavioral therapy [66], cognitive behavioral therapy [52], and acceptance and commitment therapy [67], which will be discussed later in this chapter.

Hypnosis

Hypnosis, including hypnotherapy and self-hypnosis, is a technique that has often been used in medical patients to help manage stress, increase feelings of relaxation, manage pain and nausea, and prepare for a stressful procedure [68, 69]. Hypnosis induces a state of focused concentration with suspension of some peripheral awareness. A hypnotic state includes controlled focus of an individual's attention, dissociation (i.e., the ability to compartmentalize aspects of an individual's experience), and suggestibility or heightened responsiveness to instructions [70]. Hypnosis is an intervention that is conducted by a clinician with specialized training in hypnosis, but patients can be taught to self-induce a hypnotic state to manage pain or to help tolerate a procedure. Hypnosis does not require specific equipment and is therefore easily used with patients in a medical clinic, acute hospital, or rehabilitation hospital. Hypnosis has been found to be effective in treating anxiety and stress, including anxiety related to surgery and medical procedures [71]. In a revealing study using fMRI, those who underwent hypnosis had less pain, and it was believed that this was due to pain-related sensory input not reaching higher cortical structures responsible for pain perception [72].

Biofeedback

Biofeedback is an intervention that helps individuals learn to control involuntary physiologic processes by providing information on these processes back to the individual in the form of a visual or auditory signal [73]. By monitoring physiological processes such as respiration, heart rate or pulse, peripheral skin temperature, and muscle tension, individuals can receive real-time feedback about how these physiological states respond to strategies to reduce pain or distress [74]. This approach requires some equipment to monitor physical symptoms and a computer system to help the patient practice the skill as well as clinician that has specialized training in this technique. Clinicians can seek additional training in biofeedback through programs that are approved by the Biofeedback Certification International Association. Surface electromyography (EMG) biofeedback, which is used to target and reduce muscle tension, has been found to have a moderate effect on pain for patients with various medical issues [74, 75].

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) [52] is perhaps the most studied psychological intervention used to treat a variety of psychological issues such as depression and anxiety and has been shown to be efficacious in reducing chronic pain, insomnia, anxiety, and depression in numerous medical populations. CBT is a widely used intervention with an extensive research base, including research on treatment of patients perioperatively [52, 58]. CBT is not a single approach; rather, it is a combination of cognitive and behavioral approaches that are often tailored based on the presenting issue, medical morbidity, and personal factors. There are specific manualized CBT interventions that have been adapted for patients coping with a variety of medical issues including chronic pain [76], spinal cord injuries [77], HIV disease [78], and chronic cardiopulmonary disease [79].

CBT assumes that thoughts, emotions, and behaviors are all connected and impact each other. CBT is consistent with Lazarus and Folkman's [48] transactional model of stress and typically focuses on helping the patient identify automatic appraisals of events, their feelings, and their behavioral response to those events. CBT helps patients evaluate their appraisal as helpful or unhelpful and to substitute unhelpful appraisals with more accurate, helpful ones. CBT interventions aim to create cognitive and behavioral change that promote more effective coping with negative events and improve functioning and well-being.

Cognitive Therapy

Cognitive therapy represents the "cognitive" aspect of CBT, and one of the most commonly used cognitive approaches is based on Beck's seminal work, which focuses on how people think about and interpret their experiences [52]. A primary aim of cognitive therapy is on teaching a patient to identify distorted or unhelpful thoughts and identifying more accurate or helpful thoughts to replace them. Even some thoughts that are accurate may not be helpful to a person trying to cope with a difficult situation or enjoy their life. Cognitive therapy is most often paired with behavioral therapy for a combined approach.

Behavioral Therapy

The second component of CBT includes various types of behavioral therapy [80]. Behavioral interventions are based on an underlying assumption that our behaviors or actions can impact our mood and thoughts. Behavioral therapy is based on principles of behaviorism [81] including operant learning and classical conditioning. The behavioral theory of depression relies on underlying principles of operant conditioning, a method of learning that occurs through rewards and punishments. For example, an individual may stop doing things she enjoys like seeing her friends because she feels down, and therefore seeing her friends is less rewarding. She then feels more sad because she does not have as many opportunities to do things she enjoys. This may lead her to isolate herself further, which may eventually result in a depressed mood.

In the behavioral treatment of depression, the focus is on behavioral activation and scheduling pleasurable activities like planning to try something the person enjoys at least once a day. The behavioral theory of anxiety focuses on operant conditioning and how avoidance of specific behaviors or activities, like medical appointments, further reinforce avoidance and therefore increase feelings of anxiety when they are faced with the avoided experience. These concepts are particularly applicable to postsurgical patients as they are likely not able to return to activities they enjoy immediately, and this may worsen their mood. After surgery, patients also may begin to associate different experiences with pain or nausea leading to fear and avoidance. Behavioral therapy can be used to decrease avoidance of medical visits or procedures, improve medication adherence, improve diet adherence, and reduce smoking.

Acceptance and Commitment Therapy

Acceptance and commitment therapy (ACT) [68] is a third-wave cognitive therapy where the focus is on identifying values and living a life consistent with those values. It assumes that whereas emotions can be difficult, suffering is often caused by trying to control, suppress, or deny those emotions. In this approach, individuals practice accepting their emotions as they are and planning on how to live the type of life that fits with their values instead of being guided by fear or depression. This approach incorporates mindfulness techniques as a primary way of learning to accept emotions.

Dialectical Behavioral Therapy

Dialectical behavioral therapy (DBT) [66] is a therapy originally designed to treat individuals with chronic suicidality, who often have borderline personality disorder and underlying difficulties with affect regulation and interpersonal difficulties. A full DBT program is intensive and may include multiple groups per week, individual sessions, and daily homework. While a full DBT program is not indicated for most postsurgical candidates and may be difficult for them to attend given medical issues, one component of DBT called DBT skills training may be helpful for many postsurgical patients [82, 83].

DBT skills fall into four categories: mindfulness, interpersonal effectiveness, emotion regulation, and distress tolerance. Mindfulness is similar to the mindfulness approach discussed previously. Interpersonal effectiveness skills teach patients how to prioritize their goals for interpersonal interactions and how to interact with others in an assertive and appropriate way that matches their priorities. Emotion regulation skills incorporate aspects of cognitive therapy and teach ways to moderate the intensity of emotions. Distress tolerance skills help individuals tolerate intense feelings or particularly distressing experiences without making impulsive decisions until that experience passes. These skills can be helpful to patients dealing with acute pain, a range of intense emotions following surgery, or interpersonal difficulties with family, friends, or providers that may be exacerbated by the stress of surgery.

Family Systems Interventions

Family systems interventions include several different family therapy approaches including structural [84], strategic [85], and expanded family life cycle therapy [86]. Family therapy approaches all include a focus on a system, family, or group of people instead of on an individual. These approaches focus on how systems operate and typically involve specific strategies to foster change within a family or system. These approaches typically focus on patterns of communication and relating that happen within the system and how to help the system function in a flexible manner to respond to new challenges and adapt to transitions, both expected and unexpected.

Medical family therapy is a specialized family therapy that was developed to help address medical, psychological, and family issues for medical patients. Medical family therapy is based on a biopsychosocial perspective and focuses on helping patients and medical teams to intervene at a system level (i.e., family system or medical team system) to change the dynamics that impact health and medical issues [87]. These approaches can be

Table 7.1 Psychological interventions for addressing common presenting concerns among perisurgical patients

Interventions	Type of presenting concern	Notes on implementation
Stress management skills: Diaphragmatic breathing, muscle relaxation, mindfulness, hypnosis, guided imagery, distraction	Coping with physical issue Emotional distress General adaptation after surgery Challenge to autonomy/dignity	These skills are most effective if the patient has an opportunity to practice before in acute symptoms. If this is not possible, it is best if a clinician can lead the patient through the skill and family can also learn to help patient practice
Cognitive skills: cognitive restructuring of fears or negative expectations	Coping with physical issue Emotional distress General adaptation after surgery	Focus is on challenging and restructuring unhelpful thoughts, even if they may be accurate
Behavioral techniques: distraction, engaging in pleasurable activities	Coping with physical issue Emotional distress General adaptation after surgery Challenge to autonomy/dignity	Finding distractions or pleasurable activities can be challenging in a hospital or if the patient is physically limited. Look for small things like looking out the window or looking at pictures of family that may be enjoyable or distracting
DBT skills: distress tolerance skills (self-soothing, reality acceptance skills)	Coping with physical issue Emotional distress General adaptation after surgery	Help patients identify specific ways they can incorporate these techniques
Acceptance and commitment therapy	General adaptation after surgery Challenge to autonomy/dignity	Help patients accept changes that may be difficult with a focus on how to live their lives according to their values
Family systems intervention	General adaptation after surgery Challenge to autonomy/dignity	Working with the patient and family can help improve family support to the patient, decrease conflict, and help the patient adapt to changes

helpful to medical teams and patients as they attempt to manage the common challenges and conflicts that can occur in the context of illness and surgery. Psychologists and social workers can utilize a systems focus to help both the patient and medical team navigate conflicts and patterns that may be stressful for all involved. Medical teams can help encourage communication between family members to clarify expectations for recovery and family support that may be needed (Table 7.1).

Application of Evidence-Based Therapeutic Approaches

Many of the interventions discussed in the preceding section require that patients engage in therapy over 12–16 sessions with frequent practicing of skills between sessions. Learning skills in a lower stress setting may be helpful for patients at risk for developing depression or anxiety post-surgery because it can be difficult to learn new skills and apply them in a short period of time when also coping with many issues from surgery. Presurgical evaluation is often recommended to identify patients that could benefit from preoperative interventions and to ensure that they have adequate plans for psychological and social support post-surgery. Understandably, many patients will be unable to receive a presurgical intervention due to an unexpected surgery or unexpected preoperative complications.

However, as described in the previous section, many evidence-based psychotherapies are relevant and effective for treating the kinds of psychological issues and behavioral problems encountered within the perisurgical setting. Hospital-based practice is often fraught with many real and vexing challenges. Limitations abound with respect to patient access, space, privacy, interruptions, visitors, as well as challenges related to the patient's physical condition, mental status, and the potential sedating effects of medications. A best-practice approach to psychotherapy in any setting involves the utilization of evidence-based medicine, considering clinical experience and patient values [88]. Within the perisurgical setting, flexibility and creativity are often required of clinicians as they adapt and modify therapies to meet the individual needs, preferences, and circumstances of each patient. In the following section, we review common postsurgical factors that impact the delivery of psychotherapeutic interventions.

Physical Symptoms

Patients may experience severe, unpleasant physical symptoms following surgery including pain, nausea, and torpor. Typically, these symptoms are managed medically. However, in addition to medication management, non-pharmacological psychological interventions can be helpful for coping with the distress of physical symptoms, by decreasing the hyperfocus on symptoms (appraisal) and teaching strategies (coping) to reduce fear and anxiety around physical symptoms [76].

For acute pain and nausea, stress management techniques can be helpful such as diaphragmatic breathing, muscle relaxation, mindfulness, hypnosis, and guided imagery. Stress management techniques help calm the autonomic nervous system, which can subsequently decrease the perception of pain [89]. Even just the perception of increased relaxation may be effective in moderating experiences of pain [89]. Biofeedback may be most helpful for acute pain if learned prior to surgery so that patients are able to apply the skills learned post-surgery. These approaches can be helpful for nausea, as anxiety and stress may also worsen gastrointestinal problems [89]. Likewise, patients can be taught to identify those aspects of their situation that are within their ability to control and those aspects that are beyond their ability to control. Using Lazarus and Folkman's [48] transactional model, patients would be encouraged to use problem-focused coping strategies (e.g., seeking information, active planning, decision making, and problem-solving) to help manage and cope with problems within their control. In contrast, emotion-focused strategies (e.g., seeking support, diaphragmatic breathing, meditation, acceptance) are most helpful for managing the emotions that go along with coping with problems outside of one's control.

Behavioral strategies may also be employed for coping with acute symptoms post-surgery. Distraction techniques (such as diaphragmatic breathing, guided imagery, engaging in pleasurable activities) can be helpful to reduce the amount of attention given to physically distressing symptoms. As patients may be on pain medications that make concentration difficult, it can be helpful to think of simple activities such as coloring, talking with friends or family, watching TV, and listening to music. DBT distress tolerance skills can also be helpful with acute symptoms including distracting skills, self-soothing skills, and reality acceptance skills.

Ongoing and chronic symptoms would likely benefit from a combination of cognitive and behavioral strategies that focus on coping over time. Researchers have developed specific CBT protocols for chronic pain [76] and other physical symptoms such as nausea [90]. These protocols include typical aspects of CBT such as psychoeducation about the CBT approach, scheduling pleasurable activities, and challenging maladaptive, ruminative, or catastrophizing thought processes and replacing them with more adaptive and helpful thoughts to manage physical distress. CBT also adds some unique behavioral components specifically for coping with chronic pain such as activity pacing, which is planning for a similar level of activity each day as patients with pain tend to avoid physical activity some days and then may overexert themselves when in less pain thus setting up a cycle that interferes with functioning.

Patients with co-occurring substance use disorders may require additional help managing cravings that may get elicited when receiving opioid pain medications. Multimodal and integrative therapy options should be considered. Within the postoperative setting, this may include multimodal pharmacotherapy, psychological/psychiatric support, coping skills training, spiritual support, 12-step materials, family support, physical/occupational therapy, and complementary/alternative therapies such as massage, reiki, and relaxation therapies.

Psychological Symptoms

A range of emotional reactions may occur post-surgery as patients are experiencing pain, difficulty sleeping, may be in a hospital or medical inpatient environment, and adjusting to physical changes based on surgery. While a range of emotional reactions may be normal and understandable, patients may still benefit from help moderating their emotions at this stage. Intense, difficult emotions may be overwhelming and interfere with behaviors needed for recovery including resuming activity, medication adherence, and following medical recommendations. Behavioral health clinicians may utilize motivational interviewing techniques to engage patients around addressing specific problematic behaviors. Identifying the reasons to change, potential barriers, and goals for change can occur at the bedside.

Techniques from various psychological approaches can be employed to teach patients to moderate and manage emotional distress. Many stress management techniques can be helpful to manage high-intensity emotions such as diaphragmatic breathing, progressive muscle relaxation, mindfulness, grounding skills, biofeedback, and guided imagery.

Behavioral techniques such as increasing pleasurable activities can be helpful in managing negative emotions and increase positive emotions. This can be challenging when patients have limited ability to engage in activities they enjoy due to physical limitations from surgery or because they may have difficulty concentrating on reading or games due to pain medications. Despite these challenges, even finding small things they enjoy such as talking to family or friends, listening to music, playing card games, or looking at pictures can be helpful.

Cognitive strategies can also be helpful for patients to manage emotional distress. Related to emotional distress such as sadness, anger and hopelessness are likely distorted or unhelpful thoughts. Psychologists can help patients identify these thoughts, such as “I can’t do this,” or “I will always be miserable,” and help patients create more helpful thoughts. Part of identifying new thoughts may be to consider evidence for and against current, unhelpful thoughts. Based on this analysis, patients can work to create more adaptive thoughts that are accurate but lead to less intense negative emotions and more positive emotions. For example, a patient may assume they will never lead a fulfilling life after an amputation. Working with the patient to identify their underlying assumption and evidence for that assumption can help them create a more helpful thought such as “this may be difficult, but I can still achieve many things (Table 7.2).”

Table 7.2 Common stress-induced cognitive distortions

Cognitive distortion	Explanation	Example of distortion	Example of helpful thought
All-or-nothing thinking	Something is all bad if it is not perfect	“My life is terrible if I am in pain.”	I can still enjoy spending time with my family when I am in pain
Catastrophizing	Focusing on the worst-case scenario	“My pain is the worst it could ever be and it will never go away or be controlled.”	My pain is not always the same. I have confidence that my medical team and I can control my pain so I can tolerate it
Jumping to conclusions	Anticipating a poor outcome or event when it is still unclear what will happen	“Physical therapy won’t help me walk again. Nothing ever helps me.”	“Physical therapy might help me walk again. I will try my best.”
Should statements	Any thoughts that include “should,” “ought,” and “must”	“I shouldn’t be sick.”	“I wish I wasn’t sick and I will work on improving my health.”
Personalization and blame	Believing that they are the cause for some unrelated poor outcome	“I am sick because I am a bad person.”	“Anyone can get sick, it is not a reflection of the type of person I am.”

Burns DD. Feeling good: the new mood therapy. New York: Penguin Books; 1981.

Strategies from ACT can also be helpful in managing distressing emotions. The underlying assumption of ACT is that attempts to avoid painful emotions cause suffering; therefore, accepting even painful emotions can help free people to focus on living their life according to their values [67]. This strategy may be especially helpful for patients whose emotional distress following surgery is related to limitations in physical functioning or ongoing medical issues. ACT heavily incorporates mindfulness strategies while also helping patients identify values and helps them align their life choices with their values. For patients post-surgery, re-focusing on their values and goals may make emotional distress easier to tolerate.

Strategies from DBT can also be helpful for postsurgical patients with emotional distress. Distress tolerance skills focus on straightforward skills to learn to tolerate emotional distress until it passes. Some techniques are mindfulness, self-soothing strategies, and radical acceptance. Strategies from emotion regulation skills can also be helpful in managing emotional distress including opposite action skills and building mastery.

General Adaptation After Surgery

An initial issue post-surgery for many patients is adjusting and adapting to change in physical functioning. For some patients, this may have been expected prior to surgery but nevertheless can be difficult when faced with the reality of the changes in functioning. For others, recovery post-surgery may be more difficult than they expected. Some patients may have had an emergent or unexpected surgery requiring them to adjust abruptly to the idea of surgery and recovery, as well as potentially significant long-term changes.

After surgery, patients may have beliefs about their likely recovery and future limitations that may or may not be inaccurate. A cognitive approach may be helpful to assist patients in identifying underlying beliefs about possible limitations and in challenging beliefs that are inaccurate or not helpful. For example, some people after surgery may believe that they will not be able to enjoy their life if they have physical limitations. Based on their specific situation, cognitive therapy could focus on changing expectations about recovery. For those with likely lifetime limitations, cognitive therapy could focus on beliefs that they will not be able to enjoy their life. Much research has shown that people without physical disabilities overestimate the suffering of people with disabilities and underestimate the quality of life of those with disabilities. Challenging these assumptions can help patients adjust to their new functioning and help them re-engage in activities they enjoy.

ACT may also be a helpful approach as it focuses on accepting difficult emotions and circumstances while also helping the patient focus on their values and priorities in life. This approach may be particularly helpful for those who have had an unexpected surgery or face unexpected limitations after surgery. Patients may find themselves focusing on "what if" scenarios of how their life may have been different. This type of response likely distracts them from their recovery as well as what they are able to do. By working on accepting the current situation and their emotional reaction, even if negative or unpleasant, patients are enabled to shift their focus toward goals that are meaningful to them based on their values.

Mindfulness principles, with their focus on attending to the here and now of the present moment, can also be helpful for coping with the uncertainties associated with serious illness, high-risk surgeries, and complications that may follow surgery.

Autonomy, Dignity, and Meaning

Patients recovering post-surgery may experience challenges that impact their sense of autonomy, dignity, and meaning in their life. Prior to surgery, many patients were in charge of their own schedule and accustomed to making choices about their daily activities. While recovering from surgery, patients may feel less autonomous as they are on the schedule of their medical providers and dependent on others for care. Recovering from surgery may impede patient's ability to fulfill roles that give them meaning. Patients that had previously had successful careers may find it difficult to shift to the role of patient. These types of changes post-surgery can challenge a patient's sense of autonomy, dignity, and meaning in their lives.

Addressing factors in the patient's environment can be a helpful first step in addressing issues around autonomy and dignity. Identifying the patient's specific concerns and determining if the patient can have more control in their environment or treatment plan can be helpful to address these issues. Taking time to make sure the patient's questions are addressed so they feel like they are a part of the treatment planning process can help them feel like they are actively participating in their recovery.

Behavioral strategies mentioned previously can improve a patient's sense of autonomy and dignity. Behavioral activation which is a behavioral approach that focuses on individuals planning pleasurable activities and trying to engage in pleasurable activities even when they feel down. Patients recovering from surgery are commonly limited in what they can do, but identifying even small things they may enjoy such as performing daily hygiene, ambulating (when possible), reading magazines, completing word puzzles, or talking with others can help patients feel a sense of control over their environment and buoy their sense of well-being. This can increase a patient's sense of autonomy, dignity, and the value in living.

Family systems interventions can be helpful for patients whose role in their family is changing due to recovery post-surgery. Transitions can be difficult for all involved and may cause stress not only to the patient but also to the entire family. Helping families adapt to these changes and the patient feel like they still have a meaningful role and purpose within their family can help minimize the strain to all [86].

Treatments focusing on dignity and meaning can be helpful for patients who feel a loss of meaning in their lives or a loss of dignity. Existential and humanistic therapies have a specific focus on developing meaning in one's life [91, 92]. ACT is a more recently developed therapy, which incorporates specific strategies to help individuals focus on their values and goals so they can make decisions that align with them [67]. This can be helpful for patients who are unsure how to move forward in a way that aligns with their values. Other treatments, such as dignity therapy [93] and meaning-centered psychotherapy [94], help patients nearing the end of life identify their final wishes, enhance dignity, identify sources of personal meaning, and affirm the legacy they want to leave behind.

Special Considerations

It is important to recognize that most evidence-based psychotherapies are developed under standardized conditions, using well-trained clinicians and tested on relatively homogeneous samples of patients who meet criteria for study inclusion. Although many of the therapies discussed in this chapter have been shown to be effective with diverse samples of medically ill patients, few if any have been systematically studied within the postsurgical setting and with the range of diverse patient presentations that one would expect to encounter within most surgical centers. A host of complexities related to setting, to each patient, and to unique surgery-related variables should be considered when providing psychotherapy within the postsurgical setting.

Bedside psychotherapy within hospital settings is fraught with real-world challenges, many of them related to the space and physical characteristics of the setting. Interruptions are to be expected due to noise, the limited privacy available, and exigencies of medical care. The sound of machinery, pumps, televisions, roommates, and hospital personnel may be distracting to patient and provider alike. Likewise, nurses, doctors, and other hospital personnel may require access to a patient, thus limiting the time that can be spent with a patient and nature of the psychotherapeutic work that can be accomplished. Coordination and communication with hospital personnel may help limit interruptions and enhance privacy. Likewise, it is important for behavioral health clinicians to be flexible in their therapeutic approach. Conveying empathy and meeting patients where they are (emotionally and physically), while choosing brief interventions that target the most acute and pressing issues for the patient can facilitate rapid engagement and can have the greatest therapeutic impact.

In addition, patients may be sedated, in pain, nauseous, or experiencing some other acute symptom that interferes with attention, concentration, hearing, or speech. Other patient-related considerations include sociodemographic variables, such as age, gender, gender-identity, race, ethnicity, and socioeconomic status. Each patient and patient encounter is unique. The ways in which sociodemographic variables intersect within any given individual will likely influence the individual's needs, preferences, and expectations for both surgery and postsurgical psychological intervention. For instance, postsurgical pain following a hysterectomy and oophorectomy in the setting of ovarian cancer is likely to be experienced quite differently in a childless 30-year-old woman compared to that of a 65-year-old postmenopausal woman with three adult children. Valid feelings of loss (real and symbolic) may occur within the postoperative recovery period rendering the patient vulnerable to depression, anxiety, or even a feeling of traumatization. Factoring in an awareness of other important variables such as race and ethnicity, health-literacy, social support, and prior psychiatric history will enhance a clinician's ability to accurately conceptualize the patient's needs and the ways that evidence-based therapies may need to be modified and/or individualized.

Patients with co-occurring addictions also require special consideration. The potential for abuse/misuse of addictive opiate pain medications and/or antianxiety agents should be closely assessed, and patients should be provided with appropriate effective medical alternatives to opiates or benzodiazepines. Likewise, aftercare planning is often an important component of the inpatient stay, giving careful attention to the patient's need for community-based mental health and/or addiction services. Within the pre- and postsurgical setting, behavioral health clinicians can engage patients around their mental health and addiction issues and begin appropriate relapse prevention measures to reduce risk and to build resilience.

Surgical specialties such as cardiac, organ transplant, bariatric, orthopedic, and neurosurgery often involve extensive presurgical evaluations to determine a patient's candidacy for surgery. Presurgical evaluations include the assessment of a patient's psychosocial and psychiatric history. Patient's assessed to be at-risk for stress-related postsurgical complications based on their psychosocial or psychiatric history should be provided with presurgical counseling to address the patient's expectations around the surgery while also allowing time to learn adaptive coping strategies that can be used after surgery. It is also important to identify the postsurgical physical and emotional support needs of the patient. Behavioral health clinicians may play an important role in soliciting support from family members, which is often essential to postsurgical physical and emotional recovery. Presurgical evaluations, when they can occur, benefit the patient, family, and provider by allowing time for accurate assessment of patient needs and time for proactive planning to support the recovery needs of the patient.

Summary and Conclusions

An appreciation for the mind-body connection is especially relevant within the surgical context. Surgery can be a stressful and potentially dangerous event that cannot only engender a fear of pain, disfigurement, and loss of function in many patients but also result in actual pain, disfigurement, and loss of function. In keeping with Lazarus and Folkman's [45] transactional model of stress and appraisal, one's expectations of surgery and the circumstances that led up to it can contribute significantly to the degree to which surgery is perceived as stressful. Although most patients cope reasonably well, many patients do struggle emotionally before and after surgery, particularly when the surgery is unexpected, when there is advanced illness, and when the outcome is uncertain. Patients with a history of anxiety and depression are perhaps the most at-risk for having adjustment difficulties before and after surgery. Postsurgical complications such as depression, PTSD, protracted pain, and delirium portend poorer medical and psychosocial outcomes in many realms such as postsurgical infection, rehospitalization, patient satisfaction, quality of life, and mortality.

Unfortunately, symptoms of depression and anxiety are not always reported by patients, and clinicians may not thoroughly assess for them despite clear evidence that they can negatively impact medical and surgical outcomes. Behavioral health clinicians such as psychiatrists, clinical health psychologists, rehabilitation psychologists, and social workers who practice within surgical settings and within psychiatric consultation–liaison services are in a unique position to assess and treat symptoms of stress- and health-related anxiety and depression in hopes of positively influencing a patient's postsurgical course and outcome.

Although postsurgical settings are notoriously busy with constraints on space, privacy, and patient access, important opportunities still exist for behavioral health clinicians to intervene effectively to reduce patient distress and to enhance coping and adjustment. Based on patient needs and circumstances, behavioral health clinicians can flexibly draw from a range of evidence-based psychotherapies. Effective bedside therapies within the postsurgical setting should incorporate elements of psychoeducation, cognitive therapy, behavior therapy (behavioral activation, pacing, pleasant event scheduling, DBT distress tolerance), stress management (such as MBSR), values-based therapies (ACT), and, when indicated, relapse prevention and existential/meaning-oriented therapies.

Take-Home Points

1. Depression, PTSD, substance use, and a lack of social support predict poorer postsurgical adjustment.
2. Presurgical assessments, when feasible, will help identify at-risk patients.
3. Presurgical psychoeducation, stress management and relaxation training, and skill-building psychotherapy should be provided to at-risk patients.
4. Effective postsurgical psychotherapies flexibly integrate elements of psychoeducation, relaxation training, cognitive behavioral therapy, and acceptance-based and meaning-based therapies to facilitate adaptive coping and recovery.
5. Integrated behavioral health within the perisurgical setting requires active communication and collaboration with medical personnel to coordinate care and improve patient outcomes.

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Part II

Specialties and Subspecialties

8 Psychiatric Aspects of Cardiothoracic Surgery

Walter Piddoubny and Mario Andres Caro

Introduction

Heart disease is the leading cause of death in the USA and accounts for about 17% of healthcare costs [1]. Many advances in the field of cardiac surgery have been made over past several decades including coronary artery bypass graft (CABG) surgery, cardiac transplantation, left ventricular assist devices (LVADs), automated implantable cardiac defibrillators (AICDs), and minimally invasive valvular surgeries. As the population ages, the economic burden of cardiovascular disease is expected to triple between 2010 and 2030 [1], which highlights the importance of developing strategies to prevent, mitigate, and manage co-occurring conditions in patients undergoing cardiovascular procedures.

The current healthcare environment and performance-tied hospital reimbursements are encouraging hospitals to treat the patient as a complete individual and shifting away from the "siloed" care model toward multidisciplinary care. Psychiatric conditions are common in cardiovascular surgery patients, both in the preoperative and postoperative periods, and their presence has been shown to adversely affect mortality, morbidity, length of stay, and healthcare costs. For example, depression is a common occurrence among patients with heart failure and has been associated with adverse outcomes such as increased mortality, increased healthcare utilization, worse functional status, poorer health-related quality of life (QOL), and increased frequency of hospitalizations [2–5]. Additionally, pre-existing depression has been associated with higher incidence of postoperative delirium [6, 7] in patients undergoing cardiac surgery; and delirium per se is widely known to result in adverse outcomes such as increased mortality, higher healthcare costs, and increased length of stay [8, 9].

Certain psychiatric conditions such as cognitive impairment or substance abuse can limit the patient's ability to engage in self-care and lead to poor treatment adherence, which poses challenges in patients after cardiac transplantation or LVAD implantation [2, 10, 11]. Furthermore, substance abusers often require cardiovascular surgery and present challenges such as a higher tolerance to opioid analgesics and referral to methadone or buprenorphine replacement programs.

Current literature on the interface between cardiovascular surgery and psychiatric conditions address issues like depression, anxiety, post-traumatic stress disorder (PTSD), substance abuse, cognitive impairment, and delirium. In this chapter, we will discuss psychiatric topics in

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the pre- and postoperative period in patients undergoing surgery for valvular heart disease, CABG, LVAD implantation, and AICD implantation. Psychiatric considerations in heart and lung transplantation will be discussed in a chapter on transplantation, and psychiatric considerations related to other non-cardiac thoracic surgery such as lung and esophageal cancer are discussed in the thoracic surgery chapter.

Coronary Heart Disease and Coronary Artery Bypass Surgery

An estimated 16.5 million Americans over age 20 have coronary heart disease (CHD). Mortality data for 2014 from the Centers for Disease Control and Prevention show that CHD was an underlying cause of one in seven deaths in the USA [12]. Although the rate of coronary artery bypass grafting (CABG) has been declining nationally since 1998, CABG surgery continues to be very common. According to the Society of Thoracic Surgeons Adult Cardiac Surgery Database, a total of 147,528 procedures involved isolated CABG in 2014 [13].

Delirium After Heart Surgery

Delirium is defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), as a disturbance in attention and awareness that develops over a short period of time and represents a change from baseline. An additional disturbance in cognition such as memory deficit, disorientation, language, visuospatial ability, or perception is also required [14]. The incidence of delirium after cardiac surgery ranges widely from 2% to 73% and is influenced by a host of factors such as demographic features, baseline cognitive vulnerability, and procedure type [15]. Delirium is of particular importance because it is associated with higher rates of long-term mortality [16], stroke, hospital readmissions, reduced QOL [17], poorer functional status, and cognitive decline [18–21]. Despite its impact, delirium often goes unnoticed and has non-detection rates of up to 84% [22].

Many risk factors for delirium after cardiac surgery have been identified including low preoperative cerebral oxygen saturation [23], abnormal creatinine, severe white matter hyperintensities on MRI [24], anemia, postoperative hypoxia [25], prior stroke, diabetes mellitus, duration of surgery, surgery type, red blood cell transfusion, elevation of inflammatory markers, elevation of plasma cortisol levels [26], preoperative cognitive impairment, atrial fibrillation, prolonged intubation [25, 26], advanced age, and major depressive episode [25–27]. In 2009 Rudolph et al. developed and validated the most widely used preoperative prediction rule for delirium after cardiac surgery. It includes four items, each assigned a point value. One point is given for prior stroke or TIA, abnormal albumin, Geriatric Depression Scale >4, and Mini Mental State Examination (MMSE) score 24–27. Two points are given for MMSE score ≤ 23. The incidence of delirium for point totals of 0, 1, 2, and ≥ 3 in the validation sample was 18%, 43%, 60%, and 87%, respectively [28].

Preventing Delirium After Heart Surgery

Delirium following cardiac surgery has been associated with many negative outcomes; however, there is a lack of high-quality studies for effective interventions to prevent delirium after cardiac surgery [29]. A study by Arenson et al. comparing two cardiac surgery postoperative environments—one with a lack of physical barriers between bed spaces and windowless vs. one with physical barriers for each patient and wall-to-wall windows—did not find a significant difference in delirium prevalence between cohorts [30]. In a placebo-controlled trial of 126 patients age 65 or older undergoing elective cardiac surgery with cardiopulmonary bypass, rivastigmine was not found to prevent postoperative delirium, and there was no between-group difference in the number of patients receiving haloperidol or lorazepam [31].

Choice of anesthetic agent may play a role in preventing delirium. When used to induce anesthesia, ketamine has been shown to reduce the incidence of postoperative delirium vs. placebo in patients undergoing cardiac surgery with cardiopulmonary bypass [32]. This study also noted that postoperative C-reactive protein levels were lower in the ketamine group, suggesting that ketamine may exert cognitive protective effects by reducing inflammation [32]. Dexmedetomidine, when used with morphine in patients undergoing cardiac surgery with cardiopulmonary bypass, has been shown to reduce the duration, but not incidence, of delirium [33]. When used for postoperative sedation in patients who underwent cardiac-valve operations with cardiopulmonary bypass, dexmedetomidine was found to significantly lower the incidence of delirium (3%) vs those receiving propofol (50%) and midazolam (50%) [34].

Statins have been proposed for the prevention of postoperative delirium with mixed findings. Katznelson et al. found preoperative statin use in patients undergoing cardiac surgery with cardiopulmonary bypass reduced the odds of delirium by 46% [27], whereas a similar study using preoperative statins in CABG patients found no effect on delirium rate [35].

The atypical antipsychotic risperidone has also been shown to be effective for the prevention of delirium in cardiac surgery patients. Hakim et al. showed that giving risperidone to elderly patients who experienced subsyndromal delirium (i.e., presence of one or more symptoms of delirium without meeting full delirium criteria [36]) after on-pump cardiac surgery significantly reduced the incidence of delirium when compared to placebo [37]. In fact, a randomized double-blind placebo-controlled trial of 126 patients undergoing cardiac surgery with cardiopulmonary bypass showed that a single dose of risperidone 1 mg postoperatively reduced the incidence of delirium (11.1% vs. 31.7%, $p = 0.009$) [38].

In 2015 Li and colleagues identified six risk factors for delirium after CABG, which included older age, greater comorbidity, cardiac pulmonary bypass, blood transfusion, larger transfusion volume, and longer duration of intraoperative blood pressure < 60 mm Hg. The incidence of delirium and subsyndromal delirium were 18.4% and 34.2%, respectively [39].

In a prospective trial of 92 patients undergoing CABG, Siepe et al. also found that the low mean arterial pressure group (60–70 mmHg) showed significantly higher levels of postoperative delirium and significantly greater drop in MMSE score 48 h postoperatively when compared to the high pressure (80–90 mmHg) group [40]. In addition, in a study of 113 patients, elevated perioperative plasma cortisol concentrations were associated with delirium after CABG surgery [41].

Delirium following CABG has been found to be an independent predictor of perioperative stroke, all-cause mortality, hospitalization for stroke, and longer median postoperative hospital stay (12 days vs. 6 days) when compared to those without delirium [19]. Delirium in CABG patients has been significantly associated with depression, anxiety, and stress [42]. Delirium following CABG has also been shown to be an independent predictor of sepsis [43] and mortality up to 10 years postoperatively [16]. In addition to being a risk factor for delirium [18], mild cognitive impairment preoperatively has been associated with pulmonary complications after CABG including atelectasis and prolonged ventilation [44].

Postoperative Cognitive Dysfunction

The most common complaint in the weeks following a CABG relate to memory. Rates of postoperative cognitive dysfunction (POCD) range from 33% to 83% [45]; however, some of the short-term cognitive changes may not be specific to CABG but may apply to other non-cardiac surgical procedures as well [46]. POCD is still a significant finding after CABG as its presence at 3 and 12 months postoperatively has been associated with increased mortality up to 7.5 years after CABG surgery [47].

Long-term POCD is described in this text as cognitive impairment persisting for greater than

1 year after surgery and is a common finding after CABG. In a study of 261 patients who underwent CABG, Newman and colleagues found that 53% had cognitive decline at discharge, 36% at 6 weeks, 24% at 6 months, and 42% at 5 years. Cognitive function at discharge was a significant predictor of longer-term cognition [48]. Selnes et al. described a similar finding that cognitive test scores improved from baseline to 1 year after CABG but subsequently declined significantly from 1 to 5 years [49]. In a prospective longitudinal study of 326 patients undergoing CABG assessed for POCD at 3 months, 12 months, and 7.5 years postoperatively, the prevalence of dementia and postoperative cognitive decline were 30.8% and 32.8%, respectively. Pre-existing cognitive impairment and peripheral vascular disease were both associated with dementia 7.5 years after CABG [47].

A proposed mechanism for long-term POCD is stroke, which occurs in 1–5% of CABG patients, or otherwise silent cerebrovascular events occurring perioperatively. Hypertension, diabetes, and advanced age have been identified as risk factors [45, 50]. Cardiopulmonary bypass versus off-pump CABG surgery has been investigated for contribution to cognitive decline. However, Tully et al. found no differences in neuropsychological deficits and QOL between groups [51]. Similarly, no differences in cognitive decline were found in a five-year study of 281 low-risk patients undergoing CABG between off-pump and on-pump patients [52]. Finally a meta-analysis of randomized, controlled studies comparing cognitive outcome in patients undergoing CABG with or without cardiopulmonary bypass found no significant between-group differences in cognition [53].

Cognitive decline following CABG may not differ from controls in the long-term. A study comparing cognitive outcomes using neuropsychological testing of patients undergoing CABG compared to controls without CAD showed an odds ratio of 1.37, after correction for differences in age, sex, education, and baseline comorbidity. However the decline between groups at 5 years was not statistically significant [54]**.** Other studies have demonstrated cognitive performance rather *improves* after CABG. A meta-analysis of patient performance on four cognitive tests, Rey Auditory Verbal Learning Test, trails A/trails B, digit symbol test, and grooved pegboard test, found that by 3 months after initial decline, psychomotor speed had normalized. In fact, improvement was seen in all measures relative to baseline. At 6–12 months post-CABG, significant improvement was seen in the majority of measures assessed [55].

It has also been proposed that cognitive decline following CABG may be due to comorbidities such as CAD and not the surgery itself. Selnes et al. concluded that since similar levels of cognitive decline have been observed in patients following CABG and those with CAD who have not undergone CABG, the decline may be attributed to progression of underlying cardiovascular and cerebrovascular disease. Furthermore, these authors recommend to target risk factors for cerebrovascular disease including diet, exercise, hypertension, and cholesterol to minimize the risk of cognitive decline following CABG [56].

Depression in CAD and CABG Surgery Cohorts

The rate of major depressive disorder is two- to threefold higher in patients with cardiovascular disease than in the general population. Depressive symptoms have been associated with the development of CAD, progression of CAD, and a 2–2.5 fold increased risk of mortality [57]. Depressive symptoms in elderly patients with heart failure have been independently associated with increased cardiovascular and all-cause mortality [58]. Further, depression is associated with increased mortality, nonfatal morbidity, cardiac events, poorer quality of life, and unplanned hospital readmissions. Although the biological mechanisms for this are poorly understood, disruption of the hypothalamic-pituitary-adrenal (HPA) axis, heart-rate variability, serotonergic pathways, inflammatory response, and platelet aggregation have all been proposed [7].

Depression may also play a role by decreasing physical activity. The Heart and Soul Study, which followed stable coronary heart disease outpatients for a mean of 4.8 years, found that the age-adjusted rate of cardiovascular events was 10% in patients with depressive symptoms vs. 6.7% among those without depressive symptoms. However, after adjusting for behavioral mediators such as physical inactivity, there was no significant association [59]. In a study of 436 patients awaiting non-emergent cardiac surgery, Horne and colleagues found physical inactivity to be an independent risk factor for elevated depressive symptoms preoperatively. At 3 and 6 months after surgery, physically active patients were found to have significantly lower scores on the 9-item patient health questionnaire (PHQ-9), indicative of lower depression burden. Interestingly, they also found that in patients without depression at the time of surgery, persistent physical inactivity after surgery statistically predicted new-onset postoperative depression [60].

Depression has also been shown to be a more important predictor of the success of cardiac rehabilitation than many other functional cardiac variables [61]. Meta-analysis has shown that patients with CAD have twice the risk of all-cause mortality in the 2 years after initial assessment when compared to non-depressed patients (OR, 2.24; 1.37–3.60) [62]. Despite its high prevalence and risk of morbidity and mortality, depression often goes unrecognized in cardiac patients. A survey of nearly 800 cardiovascular physicians showed that 71.2% asked less than half of their patients with CAD about depression [63].

The prevalence of unipolar major depression among CABG patients is 15–20%, which is significantly greater than the 7% 12-month prevalence in the general US population. When other types of depression (e.g., minor depression and dysthymia) are included, the prevalence in CABG patients increases to 30–40% [7, 64]. Table 8.1 summarizes studies measuring depression in patients undergoing CABG that have an $N > 100$.

Depression heralds greater morbidity and mortality for CABG patients. Depression prior to CABG has been identified as an independent predictor of cardiac hospitalization, continued surgical pain, and failure to return to previous activity at 6 months postoperatively [79]. Postoperative depression results in a more than twofold increase in hospital readmission risk following CABG surgery [80]. A study of 109 male patients assessed preoperatively with the symptom checklist-90 revised found that depression scores significantly predicted postoperative length of hospital stay ($p < 0.001$) and the incidence of late perioperative complications ($p < 0.05$). Each increase in depression t-score increased the odds of occurrence of late complications by 10% ($p = 0.018$,

Table 8.1 Prevalence of depression in patients undergoing CABG

Author	Year	*N*	Population	Diagnostic tool	% Meeting criteria for depression
Connerney et al.	2001	309	Post-op	BDI	20%
Tully et al.	2010	158	Pre-op	MINI	17.1%
Mitchell et al.	2005	137	Pre-op	BDI	28.2%
Blumenthal et al.	2003	817	Pre-op	CES-D	38%
Baker et al.	2001	158	Pre-op	CES-D	15.2%
Gallagher and McKinley	2009	155	Pre-op	HADS	16%
Borowicz et al.	2002	172	Pre-op	CES-D	32%
McKhann et al.	1997	124	Post-op	CES-D	32%
Pirraglia et al.	1999	237	Pre/post-op	CES-D	43%/23%
Krannich et al.	2007	142	Pre/post-op	HADS	25.8%/17.5%
Timberlake et al.	1997	121	Pre-op	BDI	37%
Phillips-Bute et al.	2008	427	Pre-op	CES-D	36%
Lie et al.	2007	185	Pre/post-op	HADS	19%/13%
Beresnevaitė et al.	2010	109	Pre-op	SCL-90R	23%

BDI Beck's depression index, *CES-D* center for epidemiological studies – depression, *HADS* hospital anxiety and depression scale, *MINI* mini international neuropsychiatric interview, *SCL-90R* symptom checklist-90 revised [65–78]

CI 95% 1.02–1.19) [78]. In a prospective study of 963 patients who underwent CABG, the presence of depression, as measured by Geriatric Depression Scale score ≥ 10, was found to be the single most important predictor of functional status at 6 months as measured by the Short Form-36 Physical Component Scale; it was a stronger predictor than age, history of prior MI, heart failure on admission, diabetes, or left ventricular function [81].

A nationwide population-based cohort study from Sweden found that depression was significantly associated with increased mortality in patients who underwent CABG [82]. Furthermore, meta-analysis has shown that patients with preoperative depression are at increased risk for all-cause mortality after CABG when compared to those without depression (pooled hazard ratio of 1.46, 1.23–1.73, $p < 0.0001$) [83]. A study of in-hospital mortality following CABG surgery by Dao et al found that those who were deceased had a higher likelihood of having been depressed (alive, 24.8%; deceased, 60.3%; $p < 0.001$) [84]. The mortality risk with depression following CABG appears to persist long-term. Depressive symptoms before CABG surgery have been found to be an independent contributor to mortality 2 years after CABG [85], and major depressive disorder is an independent predictor of cardiac mortality 10 years post CABG [86].

Depression following CABG surgery may persist despite surgical outcomes. Although a study by Nemati and Astaneh found that mean scores for depression and anxiety as measured by the Hamilton Depression and Anxiety Scales decreased after surgery, the effect was stronger in men than in women [87]. Furthermore, favorable surgical results after CABG surgery do not necessarily lead to a reduction in depressive symptoms [88]. As a result, patients should continue to be assessed for depression after surgery, independent of surgical outcome, and depression treated.

Depression Treatment in CAD and Heart Surgery

High-quality evidence regarding psychological and pharmacological interventions for depression in patients with CAD is limited. Meta-analysis has found that selective serotonin reuptake inhibitors (SSRIs) and psychological interventions can have clinically meaningful effects on depression outcomes but have not found that such interventions reduce mortality rates or cardiac events [89]. The Sertraline Antidepressant Heart-Attack Randomized Trial (SADHART) trial found that the SSRI sertraline was a safe and effective treatment for recurrent depression in patients with recent myocardial infarction or unstable angina [90]. Similarly, the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial found citalopram administered with weekly clinical management to be effective for treating patients with depression and CAD [91].

The data on safety for antidepressants in CABG patients are inconclusive. Several studies have shown that SSRIs do not increase the risk of bleeding or mortality [92, 93]. The Antidepressant Therapy in Patients Undergoing Coronary Artery Bypass Grafting (MOTIV-CABG) trial compared escitalopram to placebo and found no difference in morbidity or mortality up to 1 year following CABG [94]. SSRIs appear to have a negligible effect on bleeding risk when used with warfarin, antiplatelet therapies, and NSAIDs in patients undergoing CABG in the short-term [92]. However, it should be noted that SSRIs have been associated with an increased risk of upper gastrointestinal bleeding (UGIB) (OR, 1.43; 1.09–1.89), and use of PPI co-therapy can significantly reduce this risk [95].

Other studies, however, have demonstrated that SSRI use before CABG may be associated with increased risk of mortality and rehospitalization [96]. A study in Sweden comparing patients receiving SSRI prior to CABG to no antidepressant from 2006 to 2008 found increased rates for mortality and rehospitalization for heart failure, myocardial infarction, or stroke in the group taking antidepressants [97]. Patients on SSRI or serotonin/norepinephrine reuptake inhibitors (SNRIs) have been shown to be at increased risk of renal dysfunction and prolonged ventilation following CABG surgery [93].

Cognitive behavioral therapy (CBT) is the preferred type of psychotherapy for treating depression in cardiac patients. In a 12-week randomized, single-blind trial comparing CBT, supportive stress management (SSM), and usual care for depression after CABG showed that both CBT and SSM were effective, but CBT led to greater and more durable benefit [98]. A meta-analysis of psychological interventions for depressed inpatients with CAD found that only CBT showed significant effects [99]. In 2015 Hwang et al. reported on a study of patients undergoing cardiac surgery assigned to either 8 weeks of CBT or usual care. For those with an ejection fraction ≥40%, mean scores on the Beck Depression Inventory decreased only marginally, by 1.9%, in the usual care group and by 31% in the CBT group. In patients with ejection fraction <40%, BDI scores worsened by 26.8% in the usual care group and improved by 75.3% in the CBT group [100].

Collaborative care has been established as a valuable treatment option for depressed cardiac patients. In a study by Donohue et al, 189 patients who screened positive for depression following CABG on the PHQ-9 were randomized to either 8-month nurse-provided, telephone-delivered collaborative care or usual care by physician. Collaborative care was found to be a quality-improving and cost-effective treatment option [101]. In a randomized, controlled trial of 453 depressed and non-depressed post-CABG patients, Morone et al. looked at the efficacy of telephone-delivered collaborative care for depression. Depressed patients in the collaborative care group reported significantly better pain scores when compared to depressed patients in the treatment-as-usual group. Further, those with depression and at least moderate pain were found to have significantly lower functional status when compared to depressed patients with only mild pain [102]. In the Bypassing the Blues Trial, Rollman and Belnap found that post-CABG patients in the 8-month collaborative care group showed significant improvements in mental and physical health-related quality of life, functional status, and mood symptoms compared to those in the usual care group [103].

Brief educational interventions prior to admission have not been found effective for depression and anxiety prior to cardiac surgery. Shuldham et al. conducted a study of 356 patients randomized to receive either a day of education from a multidisciplinary team prior to admission for cardiac surgery vs. care as usual, which consisted of routine education on admission and throughout the hospital stay. No significant differences were found between groups in measures of anxiety, depression, and well-being either 3 days or 6 months after surgery. Curiously, the experimental group had a significantly longer length of stay [104].

Finally, statins may offer a benefit for depression. Proposed mechanisms include neuroprotection to NMDA, glutamate [105], oxidative stress, and inflammation [106]. Simvastatin may offer the greatest benefit as it has been shown to have the greatest blood-brain-barrier penetrability of the currently available statins [107]. A randomized, controlled trial comparing simvastatin to atorvastatin in patients who had undergone CABG in the past 6 months who were suffering from mild to moderate depression found that simvastatin had superior antidepressant effects [108].

Anxiety in CAD

The most common anxiety disorders in CABG patients are generalized anxiety disorder and panic disorder, with prevalence ranging from 0% to 11% [7]. Heart-focused anxiety (HFA) peaks prior to surgery and is reduced postoperatively. However, 20% of patients will continue to experience clinically elevated levels of HFA at 6-month follow-up [109]. A study of 171 patients undergoing CABG measured anxiety while awaiting surgery at home, in the hospital the day before surgery, and 3 months later. Fear and anxiety levels were highest while awaiting surgery at home. The most vulnerable populations identified were females and unpartnered patients [110]. In a study of 70 patients awaiting CABG, Fitzsimons et al. identified five main sources of anxiety: chest pain, uncertainty, fear of the operation, physical incapacity, and dissatisfaction with care offered to them [111]. Reassuringly, a significant reduction in anxiety has been shown at 3 months and 8 years following CABG surgery [88].

Anxiety has been shown to predict mortality and morbidity after cardiac surgery in general [112] or CABG in particular, after adjusting for other relevant risk factors [113]. Preoperative anxiety has been shown to lead to a more than twofold increase in hospital readmission risk following CABG surgery [80]. Premorbid generalized anxiety disorder has been shown to be a risk factor for the development of major adverse cardiovascular and cerebrovascular events (MACCE) following CABG, defined as myocardial infarction, unstable angina pectoris, repeat revascularization, heart failure, sustained arrhythmia, stroke, left ventricular failure, and mortality due to cardiac causes [114]. Anxiety increases the odds of atrial fibrillation in the postoperative period after cardiac surgery [115]. Anxiety has also been independently associated with worse cognitive performance independent of clinical CHD severity and socioeconomic variables in patients with CHD undergoing cardiac rehabilitation [116].

Post-traumatic Stress Disorder in CABG Surgery

Post-traumatic stress disorder (PTSD) is a widely underappreciated but serious comorbidity in cardiac surgery patients. PTSD is present in 14.7% of CABG patients and has been found both independently and comorbidly with depression, to increase likelihood of mortality after cardiac surgery [84]. A history of PTSD has been associated with a significant decline in postoperative cognitive function after cardiac surgery. Hudetz et al. showed that cognitive performance dropped by at least one standard deviation in 48% of patients without PTSD as opposed to 83% in those with PTSD when compared to nonsurgical controls [117]. Up to 20% of patients fail to show improvement in health-related QOL despite successful cardiac surgery. In a study of 148 patients, 18.2% had PTSD 6 months after cardiac surgery. Stress symptom scores were the most significant predictors of health-related QOL [118]. Patients with PTSD after CABG and AVR have impairments in life satisfaction and psychosocial function [119]. Notably, the use of beta-blockers after cardiac surgery with cardiopulmonary bypass may protect against the development of PTSD in women [120].

Substance Use in CABG Surgery Patients

Several studies have shown that moderate alcohol use does not increase complications or mortality in CABG patients [121–123]. A study of the Danish national registers from 2006 to 2011 did not reveal an increased risk of mortality for abstainers or moderate drinkers following CABG. Heavy drinking, however, (defined as >21 units/week), was significantly associated with increased mortality [121]. A study at Cleveland Clinic comparing patients who reported consuming at least three alcoholic drinks per week to infrequent or nonusers found that alcohol consumption was not associated with postoperative complications in patients undergoing CABG surgery [122]. A study of post-CABG patients by Mukamai et al. found no statistically significant differences in prognosis according to weekly alcohol intake: < 1 drink, 1–6 drinks, 7–13 drinks, and ≥ 14 drinks [123].

Tobacco smoking however has been shown to have significant effects on mortality after CABG. A study of 208 patients who underwent CABG found that smokers had an increased mortality as early as 3 years after surgery ($p = 0.011$) [124].

Valvular Heart Disease

The prevalence of valvular heart disease (VHD) in the USA is approximately 2.5% and rises with age, approaching 13.3% in those ≥75 years of age. There are no differences between males and females. Mitral valve disease is the most common type of VHD with moderate mitral regurgitation occurring in 9.3% of those aged 75 or older. Rates of other valvular diseases adjusted to the entire US population are aortic stenosis 0.4%, aortic regurgitation 0.5%, mitral stenosis 0.1%, and mitral regurgitation 1.7% [125].

Cognitive Disorders in VHD Surgery

Patients undergoing heart valve surgery with or without CABG have significantly higher ICU stay, hospital stay, 30-day readmission, incidence of delirium, and cognitive dysfunction 1 week after surgery compared to those undergoing CABG alone [126]. Delirium following valve surgery has been associated with longer initial intensive care unit (ICU) stay, ICU readmission, longer hospital stay, and increased mortality [127]. When compared to CABG surgery, valvular surgery patients have shown more severe neuropsychiatric deficits and a slower recovery time. Deficits for both groups are highest in fluency, arithmetic, and memory [128]. It has been proposed that the increased incidence of delirium seen after valvular surgery when compared to CABG is secondary to a higher embolic load of particulate matter and air to the cerebral circulation [129]. However, studies have yet to demonstrate conclusively that cerebral microembolizations during or after heart surgery are directly associated with postoperative cognitive impairment [130].

Depression in Aortic Valve Disease

In patients 75 years of age or older, the prevalence of moderate or severe aortic stenosis is 2.8%, and the prevalence of moderate or severe aortic regurgitation is 2% [125]. In elderly patients with symptomatic aortic stenosis, transcatheter aortic valve replacement (TAVR) has been shown to significantly improve components of mental and physical health at 9-month follow-up including physical functioning, general health, vitality, mental health, and social and emotional functioning [131]. However, predictors of worse physical and mental health after aortic valve replacement have been identified such as living alone, poor educational level, physical symptoms status, anxiety, and depression [132]. In addition to the well-established risk factors for mortality with valvular surgery such as valve position, concomitant CABG surgery, and urgency of the procedure [133], depression also appears to play a role. Approximately 29% of patients undergoing valve surgery are depressed preoperatively, and multivariable analysis has found depression to be significantly associated with mortality (odds ratio 1.90; 95% CI 1.07 to 3.40, $p = 0.03$) [134].

Delirium and Aortic Valve Replacement

The risk of delirium after aortic valve replacement (AVR) may be influenced by procedure type, and delirium occurrence has been associated with prolonged hospital stay and impaired long-term survival [135]. Transcatheter aortic valve replacement (TAVR) was approved by the US Food and Drug Administration (FDA) in 2011. According to the American College of Cardiology and Society of Thoracic Surgeons, 26,414 TAVR procedures were performed in the USA from 2011 to 2014, with 68% performed in patients 80 years of age or older [136]. In a study of 427 patients undergoing aortic valve replacement, Maniar and colleagues found the incidence of delirium was 33% for surgical aortic valve replacement (SAVR) vs. 29% for transcatheter aortic valve replacement (TAVR). TAVR by transfemoral approach had the lowest incidence of delirium when compared to alternative access techniques (18% vs. 35%, $p = 0.02$) [127]. Similar results were reported by Abawi et al. who found that risk factors for delirium after TAVR were non-transfemoral access, current smoking, carotid artery disease, atrial fibrillation, and age [135].

Rates of delirium in octogenarians are especially high and associated with even poorer outcomes. In a study of octogenarians comparing surgical and transcatheter aortic valve replacement, delirium was much commoner after open surgery (66%) vs transcatheter procedure (44%) ($p = 0.013$) even though those undergoing

TAVR were older and had lower cognitive scores and more comorbidities [137]. Another study of octogenarians undergoing surgical or transcatheter AVR found that 80% of readmissions within 30 days and 75% of patients who died within 180 days of the procedure were patients who experienced delirium post-op [138].

Infective Endocarditis and Intravenous Drug Use

Intravenous drug use (IVDU) is a common cause of infective endocarditis. Patients with IVDU have significantly higher rates of tricuspid valve involvement, poor cardiac function, embolism [139], recurrent infective endocarditis [140], fungal infection, intracranial mycotic aneurysms [141], hospital length of stay, and ICU length of stay [142] when compared to non-IVDU patients. The incidence of infective endocarditis in IVDU is 2–5% per year and responsible for 5–10% of the overall death rate [143]. IVDU is the single largest risk factor for right-sided infective endocarditis and was found in 29.5% of cases [144]. Cardiac surgery for infective endocarditis due to IVDU has a 2-year survival rate of 79% and 5-year survival of 59% [145]. Although long-term survival is similar between patients with or without IVDU, it should be noted IVDU patients are significantly younger [140]. Although younger and thus having less age-related comorbidities, these patients have higher rates of alcohol abuse, liver disease, and psychosis compared to nonusers receiving valve surgery. As shown in a study by Lemaire and colleagues, IVDU patients are more likely to develop postoperative complications including pneumonia, sepsis, kidney injury, and pulmonary embolism. They also often have less social support, are less likely to have medical insurance, and may require placement and monitoring to complete antibiotic treatment [146].

Continued IV drug use and drug overdose are the most common cause of morbidity and mortality in IVDU patients with left-sided endocarditis. Data strongly suggest that postoperative care should include treatment of drug addiction [147]. The risk of prosthetic valve endocarditis is high but can be mitigated by abstinence from drug use [145]. According to the American Heart Association guidelines from 2015, it is reasonable to treat IVDU patients with right-sided infective endocarditis medically and avoid surgery given the risk of device infection with continued IV use of substances. In all cases, referral to drug treatment program is recommended [141].

Medical hospitalization may be an opportunity to link opioid-dependent patients to treatment. Medication-assisted treatment (MAT) for opioid use disorder includes maintenance with opioid agonists (buprenorphine, methadone, combination buprenorphine/naloxone) and opioid antagonism (naltrexone). Current evidence strongly supports the use of opioid agonists, while the evidence for antagonism is weak [148]. Data on the use of MAT in hospitalized IVDU patients with infective endocarditis is sparse. A case series of 29 such patients found that the majority received opioid agonists with the goal of continuing treatment after discharge, despite not being admitted for their underling opioid use disorder [149].

Psychiatric Considerations in Left Ventricular Assist Devices (LVADs)

Left ventricular assist devices (LVADs) are the most commonly used mechanical circulatory device. The number of patients implanted with LVADs has increased over the past decade, with the Interagency Registry for Mechanical Assisted Circulatory Support (INTERMACS) reporting about 2400 LVAD implantations in the year 2014, with destination therapy (DT) being the most common indication for LVAD implantation (46%), followed by bridge to transplantation (BTT) in listed patients (30%) [150].

The pre-surgical evaluation of LVAD candidates is a multidisciplinary process. The 2013 International Society for Heart and Lung Transplantation (ISHLT) guidelines recommend a thorough biopsychosocial evaluation of LVAD candidates, with the aim to screen for the presence of cognitive dysfunction, evaluate the availability of social support systems (family, social, and emotional support), obtain a detailed psychiatric history, identify active psychiatric symptoms and the presence of current or previous substance use disorders, and discuss end-of-life decisions [151, 152].

The ISHLT guidelines also mention absolute psychiatric and social contraindications to LVAD implantation, such as inability to operate the LVAD system and answer alarms, living in an unsafe environment, poor adherence with treatment recommendations, active substance abuse or a very brief period of sobriety, and significant active psychiatric illness. Relative psychosocial contraindications include limited social support systems, poor coping skills, and lack or caregivers [2, 151]. Current guidelines do not stratify psychosocial risks and protective factors, sobriety times, or the indication for LVAD treatment. For example, a thorough psychosocial evaluation may not be feasible in patients that present in critical cardiogenic shock, as these patients require prompt treatment and may not be able to participate in medical decision-making due to the acuity of their illness. On the other hand, patients considered for LVAD as BTT require a comprehensive psychosocial evaluation, like patients evaluated for cardiac transplantation listing.

Psychiatric comorbidity is high in patients with advanced heart failure, with 20% meeting criteria for major depressive disorder [4, 5, 153], 18–45% for anxiety disorders [154, 155], and 20–23% for delirium in patients undergoing heart surgery [156, 157]. Depression in heart failure is associated with a twofold increase in mortality, increased utilization of healthcare resources, increased frequency of hospitalizations, and higher incidence of postoperative delirium in cardiac surgery [2–7], while delirium has been associated with higher mortality in cardiac patients [9].

There are limited data on the presence of psychiatric comorbidities in patients treated with LVADs. Small studies performed in patients with older generation of LVADs found a wide divergence in the prevalence of psychiatric disorders, such as depression (3–20%), adjustment disorder (37–66%), and postimplantation delirium (19–30%) [2, 158–160]. It is notable that some of these earlier studies found an unexpectedly low prevalence of depression and that there was a wide variation in the prevalence of adjustment disorders. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure Study Group (REMATCH) measured depressive symptoms preoperatively and 1 year after implantation with the Beck Depression Inventory and found statistically significant improvement in depressive symptoms 1 year after LVAD implantation [161]. Two additional groups of authors assessed anxiety and depressive symptoms in samples of 66 and 54 patients, with both studies finding improvement in anxiety and depressive symptoms after LVAD implantation [162, 163]. Both studies attributed improvement in mood to increased functional capacity and heart failure symptoms. In our sample of 123 consecutive patients implanted with LVADs at Yale New Haven Hospital, we found that 10% of patients had either current or previous major depression, whereas 8% of patients had anxiety disorders. We also found that one-third of patients met criteria for mild cognitive impairment, 6% for dementia, 13% for substance use disorder in remission, and 6% for active substance use disorders (not including smoking) [164].

The INTERMACS monitors and records adverse events in patients implanted with mechanical assist devices including LVADs. The INTERMACS records "psychiatric episodes" as adverse events, which are broadly defined as "disturbance in thinking, emotion or behavior that causes substantial impairment in functioning or marked subjective distress requiring intervention" [2, 165]. This broad definition does not allow for identification of specific psychiatric conditions, but a study of 182 LVAD recipients found that psychiatric episodes accounted for 9% of INTERMACS adverse events and that these occurred in the immediate postoperative period (≤1 week) [166].

PTSD and LVAD

PTSD has been reported after cardiac transplantation, raising questions about the possibility of development of PTSD after LVAD implantation.

One group of authors found that BTT LVAD recipients did not exhibit more postoperative trauma symptoms when compared with patients waiting for cardiac transplantation that were not implanted with an LVAD [167]. In addition, two groups of authors assessed the prevalence of anxiety and PTSD symptoms in LVAD patients and their partners, finding higher symptomatic levels of anxiety and PTSD in partners of LVAD recipients than in patients themselves [168–170].

Cognitive Impairment and LVAD

Cognitive impairment is another common malady in heart failure patients, which has been associated with poor outcomes such as hospital readmissions, increased mortality, and lower health-related QOL [171, 172]. Cognitive impairment in heart failure patients is thought to occur due to decreased cardiac output and poor cerebral perfusion. One group of authors utilized the Montreal Cognitive Assessment (MoCA) to identify patients with mild cognitive impairment (MCI), finding that 67% of a sample of 176 patients had MCI and that MoCA scores improved after LVAD implantation [173]. Given the effects of cognitive function on clinical outcomes, the guidelines from the ISHLT recommend screening for cognitive impairment preimplantation and 3, 6, 12, and 18 months postimplantation [151].

Substance Abuse and LVAD

Patients undergoing LVAD evaluation require careful assessment of their history of substance use, as the ISHLT guidelines contraindicate LVAD implantation in patients that are actively abusing substances and recommend a documented period of sobriety of 3 to 6 months [151, 152]. In practice, different LVAD centers may have different sobriety criteria, which may vary depending on the indication for LVAD implantation, with more stringent sobriety criteria for patients in which a device is considered as BTT, and more lax criteria for patients receiving an LVAD as destination therapy or as a bridge to myocardial recovery. There is one publication comparing outcomes in LVAD recipients with and without substance abuse, which found that substance abusers had a higher mortality and driveline infection rates, as well as lower rates of transplantation and transplant listing [10].

Psychiatric Treatment in LVAD Recipients

Suicide and suicide attempts by disconnecting the driveline from the LVAD system have been reported [174, 175], creating substantial challenges for the management of these patients. Nursing staff providing care for LVAD recipients require specialized training on how to operate the LVAD system, respond to alarms, and detect complications [2, 176, 177]. Staff working on inpatient psychiatric units are unlikely to have this skillset, and, therefore, LVAD recipients suffering from decompensated mental illness such as severe depression, suicidal ideation, mania, or psychosis require management on a medical floor, while a psychiatric consultant assumes the role of inpatient psychiatrist.

Recipients of continuous-flow LVADs are at a higher risk of gastrointestinal bleeding (GIB) due to changes in the small bowel microvasculature and acquired von Willebrand disease. Despite this, however, LVAD recipients require antiplatelet/anticoagulation therapy to prevent thrombosis of the pump [2, 178–181]. These facts call for careful consideration when managing depression, itself common in the heart failure population [3–7, 153], who routinely receive SSRIs, which increase rates of GIB. Multiple studies report that rates of GIB are further increased when SSRI is used in combination with antiplatelet agents or NSAIDs [182–184], but not all studies coincide on this finding [95]. Likewise, SNRIs have similar effect on platelet serotonin activity and theoretically can also result in increased bleeding risk. While routine discontinuation of serotonergic antidepressants is not recommended, clinicians should be aware of the increased risk of bleeding and carefully consider the risks and benefits of serotonergic antidepressants. Addition of proton pump inhibitors can decrease GIB risks in patients receiving SSRIs [95].

Cardiac conduction abnormalities occur in about a third of LVAD recipients and occur more frequently in the immediate postoperative period [185–187]. In line with these findings, electrocardiographic changes (e.g., QTc prolongation), as well as AICD firing, have been reported in the first week after device implantation, with normalization of QTc interval after this period [185]. The electrocardiographic changes observed after LVAD implantation and the high prevalence of psychiatric comorbidity, especially delirium, have direct implications for the use of psychotropic medication because first-generation antipsychotics, second-generation antipsychotics, tricyclic antidepressants, and even citalopram have been associated with QTc prolongation and torsade de pointes [188].

Electroconvulsive therapy (ECT) is used in patients with severe suicidality, depression with psychotic symptoms, treatment-refractory depression, catatonia, and mania, among other indications [189]. ECT often produces rapid improvement in psychiatric symptoms, but its use in patients with advanced cardiac disease or recent myocardial infarction requires careful consideration and coordination among specialties such as cardiology, anesthesiology, and psychiatry. To our knowledge, there is only one published case where a patient with treatment-refractory depression with acute suicidality (patient attempted suicide by cutting the LVAD driveline) was successfully treated with an acute series of six ECT treatments, followed by maintenance ECT for 9 months [175].

Ethical Aspects of LVAD Treatment

Mechanical circulatory support presents a myriad of ethical challenges which require special considerations in each stage of LVAD treatment [190, 191]. In non-emergent settings, a careful and thorough discussion of advanced directives, quality of life discussions, and appointment of a surrogate medical decision-maker is warranted [2, 167]. Ethical considerations after LVAD implantation include a discussion about palliative care measures, end-of-life decisions, and withdrawal of care, including LVAD deactivation [2, 191]. As is the case in patients with AICDs, deactivation of LVADs has been found to be ethically acceptable based on the principle of respecting patient autonomy (patients are allowed to refuse potentially lifesaving interventions), as long as recipients can manipulate information, understand the risks of nontreatment, and are deemed to have medical decision-making capacity [2, 26]. Circumstances in which LVAD deactivation is not ethically permissible include delirium, concerns about surrogate decision-maker (i.e., in cases where patient lacks capacity), inconsistencies in expressing treatment preference, suicidal ideation, severe depression, or significant active psychopathology [2].

Psychiatric Considerations Related to Automated Implantable Cardioverter/Defibrillators (AICDs)

Automated implantable cardioverter/defibrillators AICDs are used to terminate cardiac arrhythmias and to prevent sudden cardiac death by providing cardiac pacing or by delivering an electrical shock to the heart [192]. The groundbreaking Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) demonstrated that AICDs decrease mortality in patients with prior myocardial infarctions and low ejection fraction and in patients with heart failure and low ejection fraction [192–194]. A substantial percentage (10–54%) of patients experience AICD shocks in the first year after implantation, which can result in worse quality of life and increased psychological symptoms [195]. Multiple shocks and AICD storms occur in 10–20% of AICD patients and are associated with lower quality of life [196]. Depression symptoms affect 24–33% of AICD recipients, with one group of authors postulating that depressive symptoms may occur due to "learned helplessness." In this experimental model of depression, depressive symptoms occur due to lack of control over certain situations—in this case, a medical condition and recurrent AICD shocks [197].

Anxiety symptoms are the most commonly reported psychiatric symptom after AICD implantation, with a review article reporting increased anxiety symptoms in 24–87% of patients and clinically significant anxiety disorders in 13–38% of patients [197]. It was initially believed that there was a relationship between the number of AICD shocks and worse depression, anxiety, and quality of life, but recent studies have not replicated these findings [195, 198]. One group of authors analyzed the methodology in previously published papers on this topic and found broad methodological differences precluding a detailed analysis of their divergent findings [199].

One study evaluated longitudinal changes in psychiatric symptoms in a sample of 388 patients with AICDs, finding that 35% of patients met criteria for anxiety or PTSD at baseline, but that these symptoms improved over time and were not related to the frequency of AICD shocks [198]. A second group measured anxiety symptoms, type D personality (defined by high negative emotion), and device-related concerns in a sample of 348 patients, finding that anxiety symptoms were stable for the first year postimplantation and that type D personality was a determinant of generalized anxiety and device-related concerns [200]. In a large Swedish cohort of AICD recipients, anxiety and depression symptoms occurred more often in younger people, those who live alone, and those with prior heart failure or myocardial infarction, whereas anxiety symptoms occurred more often in females. In this study, device-related concerns were associated with worse scores in depression, anxiety, and quality of life scores, whereas the number of AICD shocks was not associated with psychosocial scores [201].

Despite the psychosocial challenges faced by patients implanted with AICDs, there are limited data discussing psychotherapies or other treatments in this field. A review on this topic identified 17 studies addressing behavioral interventions in this population and found small to modest effect sizes in improvement of depression, anxiety, and physical functioning [202].

Patients with AICDs may require treatment with psychotropics for management of various psychiatric disorders such as delirium, agitation, depression, psychosis, or anxiety. As discussed earlier, several psychotropics can prolong the QTc thereby increasing the risk of ventricular arrhythmias. Whereas AICDs prevent or treat ventricular arrhythmias, their presence signals increased risk for arrhythmias, thus warranting careful monitoring of the QTc when administering certain psychotropics [203]. Some psychotropics, such as tricyclic antidepressants, should be avoided in patients with cardiac disease due to its effect on the QTc, whereas other medications, such as antipsychotics and some SSRIs, should be used cautiously.

Take-Home Points

1. Patients undergoing CABG have a high prevalence of depression, anxiety, and postoperative cognitive impairment.
2. Cognitive behavioral therapy is the first-line treatment for depression in CABG patients.
3. Cardiac surgery, including transplantation, has been linked with development of symptoms of post-traumatic stress disorder.
4. Statins are being investigated as a possible treatment for depression in patients with cardiac disease, although at this time depression is not an FDA-approved indication for this condition.

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Psychiatric Aspects of Non-cardiac Thoracic Surgery

9

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Introduction

Non-cardiac, or general, thoracic surgeries primarily consist of procedures on the lungs or esophagus, including lung resection, lung transplantation, and esophagectomy. These surgeries may also impact the diaphragm, trachea, pleura, and chest wall. Because of the organ systems involved, symptoms of dyspnea and dysphagia are common in the perioperative period and are psychologically distressing to patients.

Dyspnea, or the experience of breathing discomfort, may be due to a variety of underlying conditions (chronic obstructive pulmonary disease, congestive heart failure, stroke, anxiety) or procedures (lung resection, endotracheal intubation). Dyspnea is detected and processed by multiple sensory and neural mechanisms (chemoreceptors, stretch receptors, muscle spindles/tendon organs). Although dyspnea has a high clinical value, its description and observation are highly subjective, so authors have worked on models of measuring dyspnea that would be objective and applicable in various clinical settings. One of these measures proposes a three-factor model and has been validated in patients with pulmonary disease and with heart disease; these three factors are work/effort, tightness, and air hunger [1]. Another measure, the multidimensional dyspnea profile, includes a significant component of emotional response, in addition to questions that prompt the patient to characterize their difficulties breathing [2].

Dyspnea can be a symptom of anxiety; alternately, it can induce anxiety or even trigger panic attacks. In a study of healthy women, the experience of air hunger was particularly influenced by psychological factors in those with high-trait anxiety [3]. Hypoxia can also manifest with signs and symptoms of anxiety [4]. Therefore, symptoms of anxiety are common in the perioperative period of thoracic surgeries, especially those impacting respiration. For example, panic disorder is more common in patients with lung transplants than in patients with heart transplants [5].

Symptoms of dysphagia, or difficulty swallowing, are also common in thoracic surgery, particularly surgery involving the esophagus. In a population-based study, intermittent dysphagia was associated with anxiety symptoms, while progressive dysphagia was associated with depressive symptoms [6]. Notably, dysphagia is associated with depressive symptoms before and after surgery for esophageal cancer [7, 8].

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Non-cardiac thoracic surgery is indicated for a variety of conditions involving trauma, cancer, and genetic diseases, and the same procedures may have multiple applications. The clinical course of psychiatric symptoms after surgical intervention varies widely, as these symptoms may improve, worsen, or remain unchanged. Postoperative psychiatric disorders in non-cardiac thoracic surgery patients are broadly associated with higher morbidity and mortality [9]. Many studies of psychiatric symptoms during the perioperative period have been pathology-specific (e.g., focusing on depression in patients undergoing esophagectomy for esophageal cancer). However, lung transplantation studies have tended to be more inclusive.

In this chapter we will first discuss surgical considerations applicable to most thoracic surgeries, including incisions and recovery. Next, we will explore the literature by pathology, examining the current understanding of the rates, significance, and, in some cases, management of psychiatric symptoms in the perioperative period.

General Considerations for Non-cardiac Thoracic Surgery

Perioperative psychiatric consultation requires a basic understanding of relevant surgical procedures. One resource for patient education produced by the Society of Thoracic Surgeons [https://ctsurgerypatients.org/] describes in non-technical language the diseases, surgical procedures, and recovery of common general thoracic surgeries.

Surgically accessing the thoracic cavity is possible via thoracotomy or sternotomy. Thoracotomy may be video-assisted, utilizing a video camera and small ports rather than the more invasive open thoracotomy. Thoracotomy and sternotomy incisions disrupt skin, muscle, and bone tissue, and the healing process is painful, sometimes chronically [10].

After thoracic surgery, chest tubes are used to drain air, blood, and fluid from the pleural space. An endotracheal tube may be left in place to facilitate mechanical ventilation, and a nasogastric tube may be placed for decompression of the stomach and administration of medications or nutrition. Postoperative management and removal of these drains and tubes can both contribute to psychiatric symptoms and be delayed by their presence.

A need for prolonged mechanical ventilation may complicate recovery from thoracic surgery, and surgical intensive care teams often seek recommendations from psychiatric consultants for difficulty weaning. Weaning from the ventilator is a complex process with numerous physiologic and neuropsychiatric considerations [11]. For example, agitation and excessive autonomic responses are barriers to weaning [12]. A psychiatric consultant can help differentiate anxiety and air hunger, which often coexist. The cycle of air hunger and anxiety can lead to conditioned responses marked by severe apprehension and avoidance.

Management of the cycle of air hunger and anxiety can be challenging in the perioperative period. Brain imaging studies of patients with dyspnea show activation of cortico-limbic areas involved in interoception and nociception [1]. Interventions that may be helpful in weaning off patients from mechanical ventilation are summarized in Table 9.1.

Tracheostomy is the creation of an airway directly into the trachea, bypassing the mouth and upper airway. It is indicated when patients have damage to the face or upper airway or to avoid long-term use of endotracheal tubes. Due to the disruption of the usual passage of air across the vocal cords, aphonia is a common complication of tracheostomy. Tracheostomy tubes can be fitted with a speaking valve to help patients vocalize. However, patients need time to learn to use these valves and build up tolerance. When evaluating or treating patients with tracheostomy, it may be helpful to simplify and shorten exam questions, combine assessments with other providers like speech and language pathology clinicians, or utilize visual analog scales and writing boards. Some neuropsychiatric assessment tools do not require patients to vocalize; e.g., the Confusion Assessment Method for the ICU (CAM-ICU) is a delirium assessment tool that

Table 9.1 Interventions that facilitate weaning off mechanical ventilation

Pharmacological agents	
Opioids Benzodiazepines	Can reduce air hunger Respiratory depressant effects can interfere with weaning
Neuroleptic medications, e.g., ziprasidone and loxapine	Can reduce agitation without reducing respiratory drive while weaning from mechanical ventilation [13, 14] May quell emotional distress; they are not anti-panic medications
Alpha-2 agonists, e.g., clonidine and dexmedetomidine	Useful in the weaning process [15]
Non-pharmacological interventions	
Biofeedback Progressive muscle relaxation	Reduce anxiety and emotional distress [16]

does not require verbal participation [17]. The Faces Anxiety Scale is a single-item self-report scale validated in the ICU population to measure state anxiety [18].

In patients with endotracheal tubes or tracheostomies, regular suctioning is necessary to remove secretions and prevent aspiration or airway obstruction. The suctioning process can induce pain, discomfort, shortness of breath, and anxiety. Notably, patients may develop anticipatory anxiety and avoidance around airway care similar to dressing changes in burn care.

During the perioperative period, many patients cannot take medications by an oral route. Familiarity with medications (e.g., haloperidol) with parenteral formulations is helpful.

The incidence of delirium after thoracic surgery ranges from 5% to 16%. Risk factors include markedly abnormal postoperative sodium, potassium, or glucose, sleep disruption, advanced age, and longer operation time [19, 20]. Readers might refer to the delirium chapter for more detailed information on the impact and management of delirium in the perioperative period. Pharmacologic approaches to delirium prophylaxis include the use of neuroleptic medications and sleep aids. As noted in a 2013 meta-analysis, a small number of studies suggested that perioperative use of prophylactic antipsychotics in the elderly may reduce the risk of postoperative delirium [21]. Ramelteon, a melatonin agonist, may also prevent delirium in the hospitalized elderly [22, 23]. Importantly, these studies were restricted to the elderly and did not focus on non-cardiac surgery patients.

Pulmonary rehabilitation (PR) is a program of treatment for patients with chronic lung disease that includes breathing exercises, education, and psychological counseling and support. In patients with chronic obstructive pulmonary disease (COPD), PR and cognitive behavioral therapy (CBT) reduced both anxiety and dyspnea symptoms in the short term [24]. Results from one study suggested that preoperative PR reduces the sensation of dyspnea and has a positive psychological effect on candidates for lung transplant [25]. However, a more recent systematic review of the effects of PR in lung transplant candidates concluded that, while some studies showed PR can improve quality of life and exercise capacity, more high-methodological-quality studies are needed [26].

The psychiatric consultant can help identify factors that contribute to nonadherence in the perioperative period. Treatments such as incentive spirometry are often indicated but can be uncomfortable. Effective interventions to improve adherence begin with a thorough assessment for delirium or cognitive impairment that limits patient understanding or ability to adhere, as well as a thorough assessment for depression that may impact patient's motivation to adhere.

Guidelines from the National Institutes of Health recommend that cancer patients be screened for depression, pain, and fatigue [27]. As is the case with many somatic illnesses, the neurovegetative symptoms of depression (e.g., loss of appetite, lack of energy, and poor sleep) are common in cancer patients, making the concurrent diagnosis of depression difficult [28]. One proposed approach to detect depressive symptoms in this population, the Endicott criteria, replaces somatic symptoms with non-somatic ones such as tearfulness, depressed appearance, social withdrawal, decreased talkativeness, brooding, self-pity, pessimism, lack of reactivity, and affective blunting [29]. However, caution is necessary when considering use of substitutive criteria sets. The measured prevalence of depression in cancer patients depends on the diagnostic instrument used [30]. Since most somatic symptoms remain important to diagnosing depression, even in palliative stages, the use of tools which narrow the concept of depression may lead to under-recognition of the need for psychological support [31].

Many pharmacological and psychotherapeutic options are available for the treatment of depression in cancer patients, although well-designed studies in this patient population are scarce. In a meta-analysis of pharmacological treatments for depression in cancer patients, SSRIs and tetracyclic antidepressants were more effective than placebo [32]; however, comparative studies of antidepressant medications were not available [33]. In a Cochrane review of antidepressants for the treatment of depression in cancer patients, extant studies did not suggest superiority of particular kinds of antidepressants for either beneficial or lack of harmful effects [34]. The tolerability of antidepressants in cancer patients is generally good. Cognitive behavioral therapy also appears to be effective in reducing depressive symptoms in cancer patients [35].

Psychiatric Issues in Common Non-cardiac Thoracic Surgery Indications

Lung Cancer and Lung Resection Surgery

Lung cancer is the second most commonly diagnosed cancer in both men and women. It is the leading reason of cancer deaths in both genders, causing an estimated 155,870 deaths in 2017. The estimated number of new cases of lung and bronchial cancer diagnosed in the United States in 2017 was 222,500, accounting for 25% of all cancer diagnoses. The incidence of lung and bronchial cancer in 2013 was 55.9 per 100,000 in men and 43.2 per 100,000 in women [36]. Non-small cell lung cancer (NSCLC) accounts for 84% of lung cancers; when caught in the early stage, surgery is usually the treatment of choice. Unfortunately, only 16% of lung cancers are diagnosed at the localized stage [37]. The 5-year survival rate for lung and bronchial cancer in the United States from 2006 to 2012 was 15.9%. The death rate for all ages of tracheal, bronchial, and lung cancers in 2015 was 47.9 per 100,000 people.

Chemotherapy, radiation, and lung resection are all potential interventions for lung cancer. Lung resection can involve removal of a focal lesion (segmentectomy, wedge resection, metastasectomy, bullectomy), lobectomy, or removal of an entire lung (i.e., pneumonectomy). In addition to lung cancer, the indications for lung resection include COPD, pulmonary metastasis, congenital abnormalities, or trauma [38].

Identifying and treating psychiatric illness in lung cancer patients is important for many reasons. Lung cancer patients with depression have worse adherence to treatment and significantly lower survival rates [39]. Lung cancer patients with anxiety and depression also have poorer health-related quality of life (QOL) [39]. Reduced social functioning, worse symptom severity, and radiation treatment are significantly associated with depressive symptoms in this population [40]. Early palliative care in patients with metastatic NSCLC improved depression scores as measured by the Patient Health Questionnaire (PHQ-9), though it did not improve survival [41]. The prevalence of depression in lung cancer ranges from 5% to 52% and varies by type [42]. In one study, the prevalence of depression and anxiety were 43% and 43%, respectively, in patients with small-cell lung cancer (SCLC) and 21% and 25%, respectively, in patients with NSCLC. In this study, depressive symptoms were strongly associated with functional impairment [43].

Park et al. prospectively examined potential risk factors for postoperative anxiety and depression after surgical treatment for lung cancer (mainly thoracoscopic resection). The authors found a postoperative increase in anxiety and depressive symptoms, as measured with the Hospital Anxiety and Depression Scale (HADS), from 8% and 9% to 12% and 19%, respectively. There was no association of gender, age, marital status, alcohol use, smoking status, preoperative comorbidities, advanced clinical stage, length of hospital stay, or pulmonary function with postoperative anxiety and depression. Thoracotomy was a risk factor for postoperative anxiety and depression, and postoperative dyspnea, severe pain, and diabetes mellitus were associated with postoperative depression [44].

Rolke et al. prospectively studied 479 newly diagnosed lung cancer patients and found that those with comorbid mood disorders had a *decrease* in anxiety and depressive symptoms after completing their first treatment modality (chemotherapy, radiation, or surgery). Patients who had had anxiety reported reduced neuropathy symptoms, and patients who had had depression reported improved social functioning and appetite. However, surgery was associated with at least temporary reduced role functioning and increased dyspnea when compared with the other treatments [45].

In a 3-month follow-up of patients with successful surgical treatment of NSCLC, the prevalence of major and minor depression was 14.8% [46]. For women who are cancer-free after surgery, up to 29% may have depression [47]. In patients with a minimum of 5 years disease-free after resection for NSCLC, 22% have distressed mood, which is associated with lower QOL [48]. In one study of 165 patients, investigators found that, after resection, tension-anxiety significantly improved while depression-dejection and confusion remained unchanged [49]. A 12-month follow-up of patients after curative resection for NSCLC found that the prevalence of depression did not change during the year after surgery, stressing the need for psychosocial support even after curative resection [50]. Although results from one study suggested that depression after curative surgical resection for NSCLC was not associated with mortality [51], in another study depression was associated with a significantly longer length of hospital stay [52]. In addition, up to 51% of patients who undergo lung resection for cancer have PTSD-related symptoms 3 months after surgery. Preoperative anxiety and postoperative pain are risk factors for PTSD symptoms [53].

Impaired cognitive function has been found in 47% of SCLC patients prior to prophylactic cranial irradiation [54] and is a risk factor for postoperative delirium. The incidence of delirium after thoracic surgery ranges from 5% to 16% [19, 20]. Ramelteon has been shown to reduce the incidence of delirium in postoperative lung cancer patients [55].

Postoperative QOL is important in patients surgically treated for NSCLC, as many do not live long. Low preoperative psychological well-being significantly predicts low postoperative QOL and poor physical and emotional functioning. Living alone also predicts poor postoperative QOL [56]. The surgical approach may also influence postoperative QOL, although results have varied. Video-assisted thoracoscopic surgery (VATS) lobectomy has numerous advantages over open surgical approaches, including shorter recovery, reduced pain and dyspnea, and improved physical functioning, independence, and overall satisfaction. In one study, QOL benefits with VATS increased with advanced age but were reduced by advanced cancer stage and comorbid illness [57, 58]. Li and colleagues compared QOL in patients with NSCLC undergoing lung resection with either VATS or thoracotomy and did not find statistically significant differences in QOL or functioning across surgical approaches [59]. Age itself may not be important for postoperative QOL; in one study, patients age ≥70 and younger patients who underwent lung resection for cancer had similar mood and QOL scores [60].

In a study of patients with unresectable NSCLC, the most common psychiatric disorders were nicotine dependence (67%), adjustment disorders (14%), alcohol dependence (13%), and major depression 5% [61]. The rate of suicidal ideation in this population is 15%; baseline pain and the development of a depressive disorder are significant predictive factors [62].

Esophageal Cancer and Esophagectomy

Unlike most types of cancer in the United States, esophageal cancer rates continue to rise [63]. Based on 1999–2013 incidence data from the North American Association of Central Cancer Registries, the number of estimated new cases of esophageal cancer in 2017 was 16,940. Unfortunately, esophageal cancer often has a grim prognosis, with a 5-year survival rate of 21% [37].

Esophagectomy is indicated for both esophageal cancer and end-stage achalasia. The procedure involves removing most of the esophagus and reconnecting the remaining portions of the GI tract. There are multiple operative approaches, with combinations of thoracotomy, laparotomy, and neck incisions. Avoidance of thoracotomy decreases the chance of respiratory complications but also decreases access to lymph nodes and surrounding tissues that may also be cancerous. Minimally invasive techniques that involve laparoscopy and thoracoscopy have also been developed. During recovery, feeding tubes are necessary to administer enteral medications and nutrition. Common postoperative complications include bleeding, infection, pneumonia, hoarseness and vocal cord paralysis, and leaks or scarring at the anastomosis [38].

The poor prognosis of esophageal cancer is associated with new-onset psychiatric symptoms, exacerbations of underlying psychiatric illness, and suicide. Data from the Swedish Nationwide Register has shown that suicide rates are higher for patients with cancers of all kinds when compared to the general population. The highest risk of suicide is in patients with cancers that have low survival rates [64]. A cohort from the Cancer Registry of Norway from 1960 to 1997 found an elevated relative risk for completed suicide in males with esophageal or stomach cancer [65]. New-onset psychiatric morbidity in patients with esophageal cancer has been shown to decrease survival, even after controlling for other prognostic factors [66]. It is therefore particularly important for clinicians caring for this population to be aware of psychiatric comorbidities that may exist.

The prevalence of psychiatric symptoms is high in patients with esophageal cancer. A study of the Taiwan National Health Insurance Research Database found that the risk of anxiety and depressive disorders requiring psychiatric intervention was higher among patients with esophageal cancer when compared to a matched cohort, with a hazard ratio of 2.24 [67]. The prevalence of probable anxiety and/or depressive disorders in patients newly diagnosed with cancer of the esophagus or gastroesophageal junction in one study was as high as 42% [68].

The prevalence of psychiatric symptoms may increase after surgery. In esophageal cancer patients awaiting surgical resection, the prevalence of anxiety was 33%, while at 12-month postoperative follow-up the prevalence was 37%. Risk factors include younger age, female sex, living alone, and severity of dysphagia. The prevalence of preoperative depression is 20–23% and increases to 32% at 12-month postoperative follow-up. In-hospital complications, limitations in activity, and severity of dysphagia are predictive of depression [7, 8].

Patients undergoing esophageal surgery may be prone to new-onset psychiatric illness requiring psychiatric treatment. In a Swedish cohort study of patients without prior psychiatric history who underwent esophageal surgery for cancer between 1987 and 2010, the 2-year cumulative incidence of psychiatric inpatient care was 2.5%; outpatient care, 4.2%; and treatment with psychotropic drugs, 32.3%. Patients with higher tumor stage were more likely to be treated in psychiatric outpatient care or with psychotropic drugs [66].

The incidence of delirium following esophagectomy ranges from 9.2% to 50% [69, 70]. Multiple risk factors have been proposed, including advanced age, irregular patterns of melatonin circadian rhythm, male gender, longer periods of mechanical ventilation, longer ICU stays, postoperative complications, and longer hospital stays [69–71]. Specific to post-esophagectomy patients in a small pilot study, using bright light therapy was found to significantly lower levels of activity, and occurrence of delirium also tended to be lower, though the difference between groups was not statistically significant [72].

As survival may be limited, QOL is an important focus of treatment. Some authors have proposed that the main sources of psychosocial stress after esophagectomy are from loss of social activity and impairment of physical capacity, less so from comorbidities such as anxiety and depression [73]. Surgical outcomes play a large role in QOL. Short- and long-term improvements in emotional function have been seen in patients who have undergone successful surgical treatment [74].

Chronic Obstructive Pulmonary Disease (COPD) and Lung Volume Reduction Surgery

COPD is the third learning cause of death in the United States, accounting for 5.7% of deaths in 2015. The most common cause of COPD is exposure to cigarette smoke [36]. Severe COPD is one indication for lung transplantation, discussed further below. Additionally, for some patients with severe emphysema, lung volume reduction surgery (LVRS) can decrease hyperinflation.

LVRS involves removing the most damaged and ineffective portions of the lung tissue, but it is somewhat controversial due to variable benefits with high potential for harm and cost. In a 2016 Cochrane review, LVRS was judged an effective treatment for selected patients with upper lobe-predominant severe emphysema and low exercise capacity, but it is associated with risks of early mortality and adverse events [75]. More recently, minimally invasive bronchoscopic approaches have been applied, including endobronchial valves, coils, and sclerosing therapies [76]. In a randomized controlled study comparing lung volume reduction surgery (LVRS) with medical treatment for emphysema, Kozora et al. found that the LVRS group had greater improvement in cognitive functioning, quality of life, and depressive symptoms at 6-month follow-up [77].

Psychiatric symptoms are more common in patients with COPD than the general population. Importantly, depressive symptoms are associated with worse respiratory specific and physical quality of life [78]. Individuals with COPD have higher prevalences of panic attacks and panic disorder than the general population, and they experience anticipatory anxiety about future attacks that are unpredictable and independent of dyspnea during COPD exacerbations [79].

Patients with COPD often experience chronic hypoxemia and show impairments in abstract reasoning, memory, performance speed, and coordination in simple motor tasks. These impairments are worse when patients have low partial arterial oxygen pressure in the blood; however, cognitive impairments are also evident in non-hypoxemic patients with COPD [80]. The prevalence of cognitive impairment in patients with COPD varies across studies, from 12% to 88% [81].

End-Stage Lung Disease and Lung Transplantation

Lung transplantation is indicated for end-stage lung disease due to COPD, cystic fibrosis, idiopathic pulmonary fibrosis, or pulmonary hypertension. These are all chronic severe conditions which often taken emotional toll on the patient and the caregivers. After COPD, discussed above, the psychiatric comorbidities of cystic fibrosis and pulmonary hypertension are most commonly the focus of clinical interventions.

- *Cystic fibrosis (CF)* is a genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), a protein involved in chloride conduction. CF is a progressive illness that predisposes patients to frequent lung infections. Antibiotics, hypertonic saline, and chest physiotherapy are mainstays of treatment, and in some cases lung transplantation is performed [82]. Substantial anxiety and depressive symptoms are common in patients with CF. In a study of adult CF patients, using the HADS, 33% had substantial anxiety symptoms, and 17% had substantial depressive symptoms. Anxiety was associated with severity of chest symptoms and difficulty in interpersonal relationships, while depression was associated with poor lung functioning and reduced quality of life [83]. In a more recent study of stable adults with CF, using the PHQ-9 and General Anxiety Disorder 7-item (GAD-7), 9.5% of patients reported suicidal thoughts. In addition, forced expiratory volume in 1 second (% predicted) was independently associated with Patient Health Questionnaire-9 depression scores [84]. Psychiatric symptoms in CF affect quality of life, healthcare utilization, and adherence. Even after controlling for lung function, anxiety and depressive symptoms are associated with worse quality of life and higher healthcare utilization [85, 86]. In children with CF, depressive symptoms are associated with nonadherence to airway clearance therapies [87].

- *Pulmonary arterial hypertension* (PAH) can result from a variety of underlying conditions, including connective tissue disorders. Management usually targets the underlying etiology, and lung transplantation may be indicated [88]. PAH is also associated with elevated prevalences of psychiatric disorders, which in turn are associated with functional impairment. Using the PHQ, Lowe et al. found that 35% of patients with PAH screened positive for psychiatric disorders, 16% for depression, and 10% for panic disorder. In keeping with the association of lung dysfunction with anxiety, patients with PAH had higher prevalences of panic attacks and panic disorder than patients with inflammatory rheumatic disease or a general primary care patient group [89].

Lung recipients have the highest morbidity and mortality of all solid organ recipients; at 5 years posttransplant 55.5% of recipients remained alive [90].

Lung transplantation may involve a single lung or both lungs, while cardiopulmonary transplantation involves both heart and lungs [91]. Thoracotomy and sometimes sternotomy are necessary for lung transplantation. The transplant surgeon performs a pneumonectomy, implants the donor lung, then connects the donor lung to the bronchi and vasculature. Not all patients require cardiopulmonary bypass, depending on their overall health status or if difficulties develop during the surgery. In the immediate postoperative period, patients require endotracheal intubation and chest tubes for drainage. The recovery process involves varying lengths of intubation and early tracheostomy placement to encourage mobility. Vigorous chest physiotherapy and physical therapy are key in mobilizing fluids and preventing weakness.

Lung transplantation requires pharmacologic treatment with corticosteroids and immunosuppressant agents, which can have significant psychiatric side effects. These issues are not unique to *lung* transplantation. The immunosuppressive regimen for most lung transplant recipients is a corticosteroid, a calcineurin inhibitor (e.g., cyclosporine, tacrolimus), and a purine synthesis antagonist (e.g., azathioprine, mycophenolate). Physicians sometimes prescribe sirolimus, but this drug is associated with anastomotic dehiscence early after transplantation.

Common postoperative complications of lung transplantation include infection, rejection, and graft failure. Infection, leaks, or stenosis can occur at the sites of anastomosis. As with all transplantation surgeries, both acute and chronic rejection are potential problems. Acute rejection is more common in transplanted lungs than in any other transplanted solid organ; while it is not usually lethal, acute rejection is a predictor of chronic rejection. Chronic rejection is currently the major limiting factor in long-term survival. In chronic rejection bronchiolitis obliterans, scarring, and fibrosis of small airways become evident [38].

As with all transplants, a pretransplant psychosocial assessment is indicated prior to lung transplantation. Behavioral health-related contraindications for lung transplantation generally include recent or current smoking, drug or alcohol use disorders, uncontrolled psychiatric illness, or nonadherence with treatment. Readers may review the chapter on transplant for more information regarding psychosocial assessments.

Awaiting organ transplantation is psychologically distressing. In a study evaluating psychiatric symptoms in patients undergoing evaluation for lung transplantation, the prevalences of current and lifetime psychiatric disorders were higher than the general population; almost 40% of patients had current anxiety disorders. Prior psychiatric history was the strongest predictor of current emotional distress, although worse lung function was also significantly associated with depressive symptoms [92].

Psychiatric symptoms may affect hospital utilization after transplant. For example, a preoperative diagnosis of anxiety disorder was associated with a higher number of hospitalizations in the first year after transplant. However, there was no association between preoperative mood disorder and length or number of hospitalizations after transplant and no association of any psychiatric diagnosis and time to initial rehospitalization after transplant [93].

The association of psychiatric symptoms with mortality after lung transplantation depends on timing. For example, pretransplant depressive symptoms and history of depression were not associated with mortality after transplant [94, 95]. Similarly, a premorbid history of anxiety was not associated with posttransplant outcome [96]. However, depressive symptoms arising shortly after transplant were associated with subsequent mortality [95]. Early posttransplant depressive symptoms were associated with an increased risk of adverse outcomes, including bronchiolitis obliterans syndrome, death, and graft loss; however, in the same study, preoperative depression and anxiety were not associated with adverse outcomes [97].

The prevalence of panic disorder is higher in lung transplant recipients compared with heart transplant recipients [5]. PTSD symptoms in lung transplant recipients are associated with younger age, lack of private insurance, exposure to trauma, and bronchiolitis obliterans syndrome [98].

Delirium after lung transplant surgery is associated with increased morbidity, mortality, and utilization of hospital resources [99]. Poorer cerebral perfusion pressure during lung transplant is associated with greater risk for delirium following transplant, as well as greater duration and severity of delirium, independent of demographic and medical predictors [100].

After lung transplantation, patients experience stable and better overall quality of life. However, with longer survival, lung transplant recipients experience greater levels of dyspnea, anxiety, and depression, with a lower level of well-being [101].

Summary

Non-cardiac thoracic surgery includes interventions for respiratory and digestive conditions with a broad range of mechanism and prognosis. Depression and anxiety are the most common psychiatric comorbidities associated with conditions that require thoracic surgery. Dyspnea and dysphagia are landmark symptoms, and they can greatly interfere with the psychiatric assessment. Mechanical ventilation, often required for these patients, can also impair communication, including the traditional psychiatric interview. Postoperatively, delirium and anxiety may have a negative impact upon recovery. Awareness of the unique challenges and significance of psychiatric symptoms in the perioperative period is key in the care of non-cardiac thoracic surgery patients.

Take-Home Points

1. Many of the illnesses for which non-cardiac thoracic surgery are indicated are associated with psychiatric morbidity.
2. Development of postoperative psychiatric disorders in non-cardiac thoracic surgery patients is broadly associated with higher morbidity and mortality.
3. Collaborate with nursing, respiratory therapy, and speech-language pathology staff when examining patients on mechanical ventilation or with a tracheostomy.
4. Carefully consider route of administration and the effects of any medications on respiratory drive in this population and where possible consider non-pharmacologic interventions.

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10 Perioperative Psychiatric Aspects in Neurosurgery

Sahil Munjal and Paula C. Zimbrean

Introduction

Every year, an estimated 22.6 million patients have neurological disorders or incur injuries that warrant the expertise of a neurosurgeon; of these, 13.8 million undergo surgery. Traumatic brain injury, stroke-related conditions, tumors, hydrocephalus, and epilepsy constitute the majority of essential neurosurgical care worldwide [1].

The practice of trepanation, which involved creating a hole in the human skull, is considered the ancient precursor of modern neurosurgery. Historians have found evidence of trepanations dating from ancient times, as far as 6500 years BC [2]. It was not until 1879, though, that William Macewen, a Scottish surgeon, reported the first successful brain tumor removal [3].

At present, neurosurgical techniques comprise many interventions for a variety of conditions, including infections, trauma, vascular disease, oncological disease, or epilepsy. The last five decades have witnessed a vast development of surgical techniques used to intervene upon the nervous system. (1) *Conventional open surgery*, which involves a neurosurgeon opening the skull, has broad modern application in trauma. (2) *Microsurgery* involves performing surgery under microscopic vision and is common in interventions on the spine or on the vascular system. (3) *Stereotaxy* consists in approaching a small target area of the brain through a minimal opening. This is used in functional neurosurgery where electrodes are implanted or gene therapy is instituted with high level of accuracy as in the case of Parkinson disease or Alzheimer disease. (4) *Endoscopic surgery* includes endoscopic endonasal surgery (used, for instance, to resect pituitary tumors or to repair cerebrospinal fluid leaks) and ventricular endoscopy (used in the treatment of intraventricular bleeds). (5) *Stereotactic radiosurgery* involves administration of radiation through localized interventions and is performed by neurosurgeons in collaboration with radiation oncologists, usually for treatment of tumors. This includes methods such as Gamma Knife or CyberKnife. (6) *Endovascular neurosurgery* uses endovascular image-guided procedures for the treatment of vascular conditions, such as aneurysms or carotid stenosis; the intervention may consist in stenting, angioplasty, clot retrieval, or embolization.

In this chapter, we will discuss conditions requiring psychiatric evaluation or treatment

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that occur in the acute neurosurgical setting. These include traumatic brain injury, epilepsy surgery, deep brain stimulation, and brain tumors.

Traumatic Brain Injury

Traumatic brain injury (TBI) is defined as an alteration in brain function or other evidence of brain pathology caused by an external force [4]. Increasing number of policy makers and researchers consider TBI a global public epidemic because it is the main cause of death and disability individuals under age 35 [5]. An estimated 69 million individuals suffer TBI from any cause each year [6]. TBI has received increased public attention in the past decade due to its reported frequency in certain popular sports, as well as recent advances in the care of the military.

Only a small portion of TBIs require surgical intervention as vast majority of mild TBI are conservatively managed. Intracranial pressure (ICP) monitoring is routinely performed in moderate and severe TBI and guides the decision to perform other neurosurgical interventions. ICP monitoring typically implies the presence of a pressure transducer that can be intraventricular, intraparenchymal, subarachnoid, or epidural [7]. Elevated ICP is defined as >20 mmHg [8]. Medical and less invasive management of TBI includes hyperosmolar therapy, ventilation therapy, sedation, infection prophylaxis, deep thrombosis prophylaxis and seizure prophylaxis, as well as cerebrospinal fluid drainage. In general, when decompressive craniectomy (DC) is recommended, a large fronto-temporo-parietal DC (15 cm diameter) is considered more effective than small DC [9].

Mechanism TBI can be produced by three main mechanisms: closed-head TBI, penetrating TBI, and blast TBI [10]. For closed-head TBI, two major factors account for trauma-related injury: (1) impact (a force makes direct contact with the skull) and (2) impulse (a force causes head movement without direct action upon the head). Studies in animal models and human injuries have investigated trauma-related factors and their effect on the extent of the TBI and prognosis. For instance, lateral head injuries tend to be more severe [11]. The mechanical injury is followed by complex biochemical events, associated electrolyte imbalances, changes in glucose metabolism and oxidative metabolism, release of cytotoxic metabolites, and cerebral edema. This may be followed by cerebral ischemia 72 h to 7 days after the surgery with immune-related axonal degeneration leading to additional damage [10]. Several experts have attempted to offer distinct description of clinical presentations in TBI according to the location of the injury in certain brain region [12]; however, due to the cascades of biomechanical and immunologic events that contribute to the development of TBI symptoms, most presentations are complex and involve more than one isolated brain region.

Measures of TBI Severity Glasgow Coma Scale is the oldest and the most widely used measure for TBI severity, and it categorizes TBI into mild, moderate, and severe [13]. Its predictive value is decreased by recent alcohol or sedative use, but GCS becomes more predictive when accounting for age and pupillary response [14]. The Marshall classification, introduced in the early 1990s, classifies TBI based on computer tomography (CT) findings including midline shift and the presence of mass lesions [15]. The Rotterdam classification added the presence or absence of intraparenchymal hemorrhage to the Marshall classification to improve its predictive value. More recently, Helsinki CT score includes only the mass lesion type and size, the presence of intraventricular hemorrhage, and cistern type [16]. Mathematic formulas allow calculations of expected 6-month mortality based on the above scores [17]. A more complex score for head trauma was developed at the Mayo Clinic—the Mayo classification system for TBI severity. This measure takes into consideration trauma-related neuroimaging abnormalities, GCS, posttraumatic amnesia, loss of consciousness, and specified post-concussive symptoms. According to this system, TBI is classified as moderate-severe (definite), mild (probable), or symptomatic (possible)

[18]; however, its predictive value remains to be demonstrated.

Psychiatric Presentations in TBI Patients

There is a bi-directional relationship between TBI and psychiatric illness. On one hand, patients with persistent mental illness are more prone to injuries in general and more likely to have a history of various degrees of TBI [19]. Conversely, TBI has been associated with an increased risk for developing psychiatric syndromes; in fact, neuropsychiatric symptoms may be present in more than 90% of patients with TBI [20]. In the long term, a TBI history increases the risk of suicide attempt [21, 22], dementia [23], and Parkinson disease [24]. Preexisting substance abuse appears to be a risk factor for developing psychiatric problems after TBI [20]. An analysis of Medicare benefits in patients with TBI hospitalized between 2006 and 2012 found that within the year after the injury, 44.8% of patients received psychotropic medications, of which antidepressants constituted 73% [25].

Other psychiatric presentations have been described after TBI: obsessional features [26], apathy (42%), irritability (37%), dysphoria/depressed mood (29%), disinhibition (28%), eating disturbances (27%), agitation (24%) [27], and impaired decision-making [28]. Due to difficulties in communicating because of the injury, TBI patients may be restricted to nonverbal communication. Whereas commonly known expressions of pain include grimacing, agitation, and increased muscle tension, studies have found that other expressions of pain may be overlooked. These include raising eyebrows, opening eyes, weeping eyes, or occasionally the absence of muscle tension [29]. Not only are psychiatric symptoms common after TBI, TBI-related psychiatric symptoms have been associated with worse outcomes. Posttraumatic psychosis is typically associated with lower cognitive functioning [30] while personality change due to TBI was associated with an inability to return to work [31].

In the immediate perioperative phase, the most common psychiatric issues are:

- *Sleep disturbances*. In a recent meta-analysis ($n = 637$), TBI patients had poorer sleep efficiency, shorter total sleep time, shorter REM latency, and greater wake after sleep onset [32]. Additionally, disturbances in the circadian melatonin have been found, which may explain sleep disturbances commonly found in these patients [33].
- *Delirium.* A recent study found that even after TBI of only mild-to-moderate severity, roughly half of patients developed delirium in the first 4 days after trauma [34] while rates of delirium up to 86% have been reported among TBI patients in the ICU [5].
- *Agitation*. Agitation is a common symptom reported in TBI patients and often the reason for psychiatric consultation. A prospective study of 158 subjects found that approximately 50% of patients display agitation in the acute setting. Agitation typically lasted less than 10 days and was without gender differences [35]. Notably, tramadol increases incidence of agitation as well as ICU and hospital length of stay after TBI [36].
- *Mood disorders*. In a study of 559 TBI patients followed up to a year post injury, 6.3% developed persistent depression, 13.2% had delayed depression, 10.4% had depression recovery, and 72.1% had low level of depression [37]. For patients more than a month after TBI, risk factors for developing depression include perceived stress, ongoing pain, and litigation status [38]. Preexisting alcohol abuse and a left parietal lobe injury were more likely to be associated with a decline in psychiatric status 6 months after the TBI [39]. A study of 68,376 TBI patients without pre-injury mental illness showed that these patients were at a higher risk of bipolar disorder and major depressive disorder than the general population. Depression was more likely to occur the first year, whereas symptoms of bipolar depression were more likely to occur between 2 and 4 years post injury [40]. Depression after TBI is often undertreated [41]. Even if depression in TBI develops after the immediate perioperative phase, recent studies suggest the possibility of reducing its incidence with early

postoperative interventions as we will discuss below.

- *Acute stress disorder/posttraumatic stress disorder (PTSD)*. The rate of PTSD after severe TBI has been reported at 27.1% [42] and 15.3% in patients after mild TBI [43]. For PTSD, a briefer period of posttraumatic amnesia (PTA) is associated with increased symptoms of PTSD. Even still, PTSD has been reported in patients who had a posttraumatic amnesia longer than 1 week [44]. Early symptoms of heightened arousal and disengagement were independent predictors for development of PTSD 2 months after trauma [45].

For combat-related mild TBI, four clinical subtypes of posttraumatic psychiatric trajectories have been described. These include (1) a psychiatric group consisting mainly of PTSD (21.9% of the sample), (2) a cognitive group presenting with primarily cognitive and headache complaints and few mood symptoms (21.5%), (3) a mixed profile group presenting with a combination of mood and cognitive complaints and headaches (18.6%), and (4) a good recovery group with low symptom profile (37.8%) [46].

Psychiatric Interventions in TBI Patients

In the perioperative phase, two treatment targets for psychiatric intervention may be considered: management of acute symptoms or interventions that may reduce the risk of psychiatric symptom onset later in the course of illness.

In treating psychiatric symptoms associated with TBI, it is important to become familiar with the general neurosurgical/ICU treatment of these conditions because several general recommendations may be directly relevant. For instance, recent guidelines from the Brain Trauma Foundation emphasize the importance of maintaining systolic brain pressure above certain thresholds (depending on age) [9]. Therefore, psychotropics that can lower the blood pressure should be used cautiously. Although corticosteroids, which are associated with dose-dependent psychiatric side effects, were used liberally in the past, they are not currently universally recommended to reduce intracerebral edema. In addition, prophylactic use of antiepileptics is no longer recommended in all cases, since early posttraumatic seizures are not associated with worse outcome [9]. A recent study has shown that poor glycemic control in the acute phase of TBI treatment may lead to neuronal dysfunction and cerebral edema, which advocates for tighter glucose regulation [47]. This is relevant when atypical antipsychotics, known for their risks of impairing glycemic control, are considered. For delirium in TBI patients, general recommendations to address contributing factors (e.g., sepsis, use of deliriogenic medications) and implement non-pharmacological interventions still apply, as discussed in detail in Chap. 4.

Evidence for use of psychotropic medications in TBI patients is limited to animal studies or human case reports, cohort studies, open studies, and very small prospective studies. At this time, there is no FDA-approved medication for TBI-related psychiatric symptoms.

Treating agitation acutely after TBI often starts with sedation, while the patient is mechanically ventilated. Dexmedetomidine and propofol appear equally effective in sedating severely brain-injured patients, and neither is associated with adverse physiological effects as measured by multimodal monitoring [48]. However, a growing body of literature in other settings suggests that dexmedetomidine is associated with a lower risk of delirium than propofol. For treatment of agitation in TBI, multiple agents have been explored including benzodiazepines, estrogens, antiandrogens, neuroleptics, antidepressants, antiparkinsonian agents, anticonvulsants, lithium carbonate, buspirone, beta-blockers, psychostimulants, and alkylphenols [49]. A recent European position paper summarizing a systematic review of literature and expert opinion suggests beta-blockers (evidence level B) and anticonvulsants (valproic acid and carbamazepine, evidence level C) as first-line treatment. Neuroleptics, antidepressants, benzodiazepines, and buspirone are cited as second-line considerations based on expert opinion [50]. Neuroleptics are a common choice due to their sedative effect; small studies reported positive impact on agitation with loxapine [51], ziprasidone [52], quetiapine [53], and aripiprazole [54]. Neuroleptics should generally be discontinued as soon as possible [50] because several studies have suggested that antipsychotic use may decrease the effect of rehabilitation [55], especially if used long term [56, 57].

Among agents used to increase arousal for patients in vegetative state or minimally conscious states, amantadine has shown the most promising results, including positive trend in a randomized placebo-controlled trial [58]. Sertraline, methylphenidate, modafinil, zolpidem, and naltrexone were helpful only in isolated case reports or open studies [59]. Use of amantadine in TBI patients in the ICU was initially thought to reduce agitation and improve cognition [60]; however, it was also associated with greater opioid use and a longer ICU length of stay [61]. Melatonin appears safe and effective for sleep disturbances in TBI patients [62]. For fatigue after TBI, modafinil was not found to be helpful, whereas piracetam (not available in the USA) and light therapy with short-wavelength, blue-appearing light have shown promising results [63].

A growing body of literature suggest a neuroprotective role of lithium. Lithium has been shown to reduce neuronal death, microglial activation, and cyclooxygenase-2 induction and to preserve blood-brain barrier integrity. Though its efficacy in clinical settings remains unproven, it has been theorized to mitigate neurological deficits and psychiatric disturbance and improve learning and memory outcome [64].

Sertraline may prevent depression after TBI [65]. In fact, one study has suggested that sertraline may even improve cognitive function when used to treat post-TBI depression [66]; however, it remains unclear whether sertraline improved cognition per se or whether it improved depression, thereby alleviating the influence of depression on cognitive performance [67, 68]. Further, the use of SSRIs deserves caution in this population because they may increase the risk of hemorrhagic stroke [69]. An open-label study investigated the role of genetic factors as predictors to response to antidepressants in TBI patients. Single nucleotide polymorphisms in the genes *MTHFR* and *BDNF* predicted greater treatment response, while a variant of the *5HTTLPR* gene predicted greater likelihood of adverse events [70]. Interestingly, a retrospective study found that early treatment with beta-blockers is associated with reduced incidence of depression after TBI [71].

A handful of non-pharmacological interventions have been studied to address TBI-related psychiatric and cognitive sequelae. A recent systematic review indicated that computerized interventions for cognitive rehabilitation may improve attention and executive function [72]. An 8-week program of mindfulness-based cognitive therapy showed a significant effect on depression, pain intensity, and energy levels in individuals with TBI [73]. Cognitive behavioral therapy and mindfulness-based cognitive therapy have been reported to improve depression after TBI [74].

Due to the high comorbidity of psychiatric symptoms in patients with brain injury, multidisciplinary programs that address the complex needs of this patient population in a community setting are generally recommended [75].

Epilepsy Surgery

Epidemiology

In 2015, 1.2% of the US population had active epilepsy, accounting for 3.4 million people with epilepsy nationwide [76]. Even though a majority of persons with epilepsy achieve acceptable seizure control with antiepileptic drugs (AEDs), approximately 30–35% of patients with seizures have drug-resistant epilepsy (DRE) [77, 78], which is defined as failure of two or more AEDs given at adequate doses in a patient who has received an accurate diagnosis of epilepsy (i.e., psychogenic non-epileptic seizures being ruled out) [79]. Multiple cross-sectional studies have shown that improvement in quality of life (QOL) is associated with seizure freedom rather than decreased seizure frequency [80]. In spite of the increased probability of seizure freedom with appropriate surgical intervention and subsequent impact on QOL, of the 750,000 patients in the USA with DRE, only 1500 undergo epilepsy surgery per year [81]. Persistent seizures negatively affect psychosocial, educational, and occupational domains of life [82].

Seizure freedom occurs in 55–70% of individuals undergoing temporal resection and 30–50% undergoing extratemporal resection [83]. True "cures" defined as being seizure-free without AEDs are reported in 25–28% patients following epilepsy surgery [84, 85]. For selected patients, epilepsy surgery is an effective therapeutic option for refractory focal epilepsy.

Interestingly, only 1% of patients with DRE are referred to full-service epilepsy centers annually where multidisciplinary epilepsy specialists can explore advanced treatment options including surgical candidacy [86]. Further, for those patients who do ultimately undergo epilepsy surgery, the delay from onset of epilepsy to surgery averages over 20 years [87]. Cognitive, psychiatric, QOL, and psychosocial outcomes of epilepsy surgery are less clearly defined and may be of substantial concern to patients and referring neurologists [88].

The number of US epilepsy centers offering surgical therapy has increased over the years [89], which makes it all the more important for the psychiatrist to have knowledge regarding psychiatric aspects of epilepsy surgery. Psychiatrist participation is considered essential in the surgical decision making to select candidates and to minimize psychiatric sequelae. Psychiatric input can help to anticipate likelihood of adherence with medications, assess the degree to which patient's expectations after surgery are realistic, explore the nature of a patient's social support, and evaluate for personality, psychotic, or mood disorders. In a comprehensive model of care, pre-surgical psychiatric and psychosocial evaluation aids the epilepsy team by assessing a patient's capacity to consent as well as cope with the surgery [90].

Types of Surgical Intervention for Epilepsy

Several types of surgical interventions for epilepsy are available:

- *Lobe resection*. Certain portions or entire lobes of the brain may be resected depending on where the seizure focus is located. Temporal lobe epilepsy, in which the seizure focus is within the temporal lobe, is the most common type that benefits from this intervention. Extratemporal resection involves removing brain tissue from areas outside of the temporal lobe.
- *Lesionectomy*. This surgery removes brain lesions including areas of injury or defect such as a tumor or malformed blood vessel that generates seizures.
- *Corpus callosotomy*. The corpus callosum is a band of nerve fibers connecting the two hemispheres of the brain. The effect of this surgical procedure is to stop communication between the hemispheres and prevent the spread of seizures from one side of the brain to the other.
- *Functional hemispherectomy*. In a hemispherectomy, the entire hemisphere is removed. In a functional hemispherectomy, the hemisphere is left in place but disconnected from the rest of the brain.
- *Multiple subpial transection (MST)*. This procedure can help control seizures that begin in areas of the brain that cannot be safely removed. The surgeon makes a series of transections in the brain tissue. These cuts can interrupt the flow of seizure impulses but do not disturb normal brain activity.
- Two semi-invasive ablation procedures have been introduced recently: *radio-frequency thermocoagulation* [91, 92] and *laser intermittent thermal ablation* treatment. These are increasingly used in the USA but are not yet approved in Europe [93, 94].
- *Neurostimulation*. For patients with refractory epilepsy who are not candidates for resection, neurostimulation, which entails the electrical modulation of epileptogenic brain tissue, is an emerging treatment alternative. Several forms

of neurostimulation are currently available. Invasive therapies include vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS). Current evidence supports stable cognition and mood with all currently available neurostimulation therapies, and in some instances cognition and mood may even improve with these interventions [95].

The Pre-surgical Evaluation for Epilepsy Surgery

Patients considered for epilepsy surgery should typically meet the following criteria: disabling seizures that have not been controlled by adequate trials of appropriate AEDs without adverse side effects [77] and clinical, neuroimaging, or electroencephalographic (EEG) evidence of an epileptogenic brain region that may be safely resected [96]. If no focal region is identified, the seizures must be disabling enough to warrant a palliative surgical procedure [97, 98].

A thorough history is the first and most important step in the evaluation of an intractable seizure disorder to identify the seizure semiology. Video EEG (vEEG) monitoring must be performed to record seizure episodes and to confirm their concordance with the historical, routine EEG and MRI data. vEEG monitoring may also reveal psychogenic non-epileptic seizures or detect seizures that arise from areas other than the presumed site. An epilepsy protocol MRI, which can reveal common seizure substrates such as mesial temporal sclerosis (MTS), cortical dysplasias, and cavernous hemangioma, is also typically performed [99].

Neuropsychological assessment is important for documenting cognitive status, identifying potentially reversible causes of functional impairment, and informing postsurgical cognitive outcomes [100]. Among its many purposes, it provides lateralizing and localizing information. It is also used as a general determination of baseline (preoperative) neurobehavioral status [101]. Some types of neuropsychological dysfunction such as verbal memory impairment are associated with left TLE [102]. More importantly, the degree of preoperative verbal memory impairment is a strong predictor of postoperative memory decline following surgery in the dominant temporal lobe [103, 104]. Presence of diffuse neuropsychological deficits may be an indicator of extensive brain disease and therefore suggests poorer outcomes following focal resection. Most neuropsychologists also evaluate psychiatric symptoms, but traditionally this has not been a focus of intervention by the epilepsy team.

Psychiatric Symptoms in Epilepsy

Studies have reported a 20–40% prevalence of comorbid psychiatric disorders in patients with refractory temporal lobe epilepsy and mesial temporal sclerosis (TLE-MTS) and up to 70% in those with refractory forms of epilepsy [105–110]. Although the majority of studies find increased psychiatric morbidity among patients with epilepsy in both children and adults, the relationship between type of epilepsy, seizure focus, and nature of psychiatric disturbance remains controversial with inconsistent evidence [111]. Mood disorders are the most common (24–74%), followed by anxiety (10–25%), psychotic disorders (2–9%), and personality disorders (1–2%) [106–109]. Given the high prevalence of pre-surgical psychiatric disorders in this population, the psychiatric outcomes of such patients have become of particular interest to researchers [107, 108].

Compellingly, the correlation between the presence of pre-surgical psychiatric disorders and worse postsurgical seizure outcomes in patients with refractory epilepsy who underwent surgery has been increasingly recognized [109, 110, 112–116]. To the contrary, a recent multicenter, prospective study found no such association between pre-surgical psychiatric illness and likelihood of attaining long-term seizure-free surgical outcome [117]. In general, preexisting psychiatric disorders can complicate the postoperative course due to (a) postoperative symptom exacerbation (e.g., depression, psychosis) [113], (b) reduced ability to adapt to perisurgical and postsurgical care (e.g., personality disorders) [118], and (c) the potential risk of an association with poorer seizure-related outcomes [119]. Epilepsy surgery teams, ideally in collaboration with psychiatry, should discuss how to mitigate these potential complications prior to embarking on surgery and also monitor closely for them in the peri- and postoperative setting [120].

Patient selection for surgery is important because pre- and postoperative psychiatric morbidity are related. Many epilepsy centers currently exclude patients with a psychotic illness from epilepsy surgery. For those patients who experience postsurgical psychosis, one expects that the majority of these represent relapse of a preexisting psychotic illness than de novo psychosis as a result of the surgery, yet a history of psychosis should not be considered a contraindication to epilepsy surgery. Patients with psychotic disorders can often cooperate during the pre-surgical evaluation, develop a functional understanding of the surgical procedure, and provide informed consent [121]. It is a misconception that chronic psychosis is a contraindication to surgery, and these patients may benefit if seizures are eliminated [122]. If a patient has active psychiatric symptoms including psychosis (which may itself be related to epilepsy), the surgical procedure can often be postponed until these symptoms are sufficiently stable so that the patient can withstand the stresses of surgery [120].

Psychiatric Outcomes After Epilepsy Surgery

With only 3% of all studies of epilepsy surgery outcomes reporting psychiatric outcomes [123], data on the relationship between epilepsy surgery and psychiatric outcomes is very limited [124]. Ideally, psychiatric follow-up of patients in epilepsy surgery programs should be prospective and longitudinal, with a preoperative assessment and structured follow-up. The method of psychiatric evaluation differs between studies. While some investigators use only screening instruments (especially for depression and anxiety), others use structured psychiatric interviews and include information from family members (and occasionally medical staff) as a basis for formal psychiatric diagnoses. Whereas rating scales typically gauge self-perceived psychiatric symptoms during a brief period, structured psychiatric interviews may ascertain lifetime as well as current psychiatric diagnoses [99].

Psychiatric Symptoms in Patients with Epilepsy and Postoperatively

Depression Pre-surgical depression has a prevalence of 5–50% among patients who will undergo epilepsy surgery [123]. Interestingly, pre-surgical depressive symptoms may be associated with an increased risk of postsurgical memory decline [125]. Findings on whether depression is related to successful postsurgical control of seizures are inconsistent [105, 126].

Postsurgical anxiety and depression are observed in 10–30% of patients [123, 124, 127]. Depressive disorders following an antero-temporal lobectomy in particular have been increasingly reported [128]. Additionally, "mood lability" is not uncommon within the first 3 months after surgery, and up to 30% of patients will experience overt symptoms of depression within the first 6 months. On the other hand, other studies have reported that both depression and anxiety symptoms may rather improve after epilepsy surgery [129–131]. Reassuringly, such postoperative mood-related symptoms, when they do occur de novo after surgery, typically subside with time.

Existing evidence on the effectiveness of antidepressants in treating depressive symptoms associated with epilepsy is very limited. Authors have suggested, though, that depression in this context often responds readily to antidepressant medication [121]. Readers are referred to a consensus statement by Barry et al. outlining the use of psychometric tools for diagnosis of affective disorders and a stepwise approach to treatment for people with epilepsy [132]. Patients may be understandably reluctant to take "more medications," especially if they have heard that psychotropics carry a potential proconvulsant risk. It is important to counsel patients that several studies have found that antidepressants are often effective without an increased risk of seizure occurrence when used at therapeutic doses [133–135]. Curiously, patients with frequent seizures may even experience a decrease in seizure frequency while on SSRIs and SNRIs [136].

A Cochrane review was unable to identify high-quality evidence to inform the choice of antidepressant drug or drug class in treating depression in people with epilepsy. There is low-quality evidence of safety in terms of seizure exacerbation with SSRIs and no available comparative data on antidepressant classes and safety in relation to seizures [137]. In general, SSRIs are safe in patients with epilepsy and should be used first line [138]. Preference should be given to SSRIs that have minimal effects on the CYP 450 system because supra- or subtherapeutic levels of hepatically metabolized AEDs can lead to toxicity or loss of effect, respectively. Antidepressants known to increase risk of seizures include amoxapine, clomipramine, bupropion, and mirtazapine [139, 140].

In severe treatment-resistant depression after epilepsy surgery, especially when suicidal risk requires rapid intervention, electroconvulsive therapy (ECT) has been used safely and successfully [141, 142].

Anxiety The prevalence of anxiety symptoms is higher in patients with epilepsy than in the general population or in patients with several chronic medical disorders, but anxiety disorders often go unrecognized or untreated [143]. Multiple studies have reported anxiety disorders in patients in pre-surgical assessment with rates of 10–25% [129, 144–146].

Anxiety symptoms often occur in the early postoperative period, often before manifest depression develops [145]. In fact, symptoms of anxiety and fear of variable severity have been reported to occur in about 40% of patients [120]. Only a few longitudinal studies have followed patients postoperatively, but those that have identified an early postoperative increase in anxiety disorders with most symptoms having remitted at 3 months [129, 145, 146].

SSRIs and SNRIs are considered the first line for management of anxiety in epilepsy patients. Short-term use of benzodiazepines (BZD) can be considered. They act on the GABA receptors and may not only increase the threshold for seizures but also control anxiety by reducing neuronal excitability [147]. However long-term use is discouraged, not only due to the risk for dependence and sedation but also to the hyperexcitability phenomenon in an interdose time which may increase seizure episodes [148].

Obsessive Compulsive Disorder (OCD) In a recent study of 62 patients with temporal lobe epilepsy, 14.5% were diagnosed with OCD compared to 1.2% of healthy controls [149]. Results have been mixed regarding epilepsy surgery and improvement of OCD-related symptoms [150, 151].

Mania Mania in epilepsy is quite rare and occurs most often in the context of postictal psychosis [152, 153]. However, mania has also been observed postsurgically in a small subset (~10%) of epilepsy patients, usually within weeks of surgery with a relatively transient course [152]. The risk for development of postoperative mania is highest among patients who undergo right temporal lobe resections [153, 154].

Psychosis Pre-surgical psychosis, unrelated to seizure activity, has a prevalence of up to 16% in epilepsy patients [123]. The rate of de novo postoperative psychoses is especially low, affecting about 2% of patients after epilepsy surgery [155]. In patients with a suspected primary psychotic disorder, some authors have recommended adding low-dose risperidone (1–2 mg/day) before overt psychotic symptoms appear to prevent psychiatric decompensation in the surgical setting [156]. As for severe depression, reports have documented safe, effective use of ECT in the management of severe postoperative psychosis [157].

As mentioned earlier, comorbid psychosis in patients with refractory epilepsy should not constitute a contraindication to epilepsy surgery [158]. In fact, patients with psychosis may stand to experience even greater benefits with the surgical procedure, though such patients should be closely supervised by a psychiatrist [159].

The seizure rate associated with the use of antipsychotic drugs has ranged from 0.5% to 1.2% among non-epileptic patients [160]. The risk is higher in the presence of the following factors: (1) a history of epilepsy, (2) abnormal EEG recordings, (3) history of CNS disorder, (4) rapid titration of the antipsychotic dose, (5) high-dose antipsychotic, and (6) the presence of other drugs that lower the seizure threshold [161]. Clozapine has been reported to cause seizures in 4.4% of patients when used at doses above 600 mg/day, whereas at doses lower than 300 mg/day, the incidence of seizures is less than 1% [162]. A FDA summary showed increased seizure incidence with clozapine, olanzapine, and quetiapine [163]. Clinicians should also be mindful of the induction of hepatic enzymes by the enzyme-inducing AEDs, which may increase the clearance of some antipsychotics thereby risking psychotic decompensation [121].

Suicide A meta-analysis revealed that suicide in patients with epilepsy after surgical treatment is up to 13 times more common than in the general population [164]. A study investigating suicide outcomes after resective epilepsy surgery suggested that good seizure control after a successful surgical resection does not eliminate the risk of suicide [165]. Even successfully treated patients should be monitored, supported, and transitioned into wellness [166]. However, these findings may be related to confounding by indication. For instance, a recent prospective study assessing psychiatric outcomes in DRE found that surgical cohort experienced a significant decrease in psychiatric symptoms relative to those who were only maintained on the same AED regimen. In addition, distress perception also improved only in surgical patients [167].

Cognitive Deficits The overall goal of epilepsy surgery is to achieve seizure control with minimal effect on the functional integrity of tissues or fiber tracts, which is why targeted surgical procedures are usually preferred [168]. Word-finding difficulties and memory deficits occur in 20–30% of patients, especially after temporal lobe resections of the language-dominant side, and these changes may be permanent [169]. Verbal decline is the most consistent adverse effect on functioning after left temporal resection [170–173]. Verbal memory deficits and diminished ability for naming items are observed [171]. In a meta-analysis, 44% of patients with left temporal resections and 20% of patients with right temporal resections sustained a decline in verbal memory naming deficits, as distinct from verbal memory, were present in 34% of patients with left-sided resections [174]. Right-sided temporal lobe resections are not associated with nonverbal memory decline [172, 175]. Intellect is not affected by temporal lobe surgery [173, 174]. Age at surgery and pre-surgical level of cognitive function influenced cognitive function after temporal lobe resection [103].

Current data do not allow for definitive statements about which surgical approaches may influence neuropsychological outcome [168]. Even though temporal lobe resection is associated with some cognitive decline, continued, uncontrolled seizure activity can also result in increasing neuropsychological deficits. After 10 years of observation, memory decline was the same in medically and surgically treated patients. Cognitive decline acquired with surgery may be similar to the long-term cognitive decline associated with continued seizure activity [176]. In contrast to cognitive deficits that may occur following temporal lobe resection, resection of non-temporal lobe brain regions has not been associated with cognitive deficits; however, these data remain preliminary and, therefore, inconclusive [174].

Psychosocial Factors and Quality of Life (QOL) in Epilepsy Surgery

Two separate randomized clinical trials (RCTs) for epilepsy surgery found significantly improved QOL attributable to epilepsy surgery. However, improvements in QOL were not sustained over time [82, 177]. Recently published QOL results from a large multicenter trial demonstrated that improved QOL after surgery is heavily dependent on achieving an improved seizure-free outcome [80]. Also, patients who have medically resistant epilepsy and comorbid depression or anxiety generally experience improved QOL with successful epilepsy surgery. Overall QOL is determined by the absence of clinically significant psychiatric symptoms and stability in the community [178]. Preoperative expectations influence postoperative course. The more concrete, practical, and realistic the postsurgical expectations are before surgery, the better postoperative QOL experienced [179].

The psychosocial factors affecting QOL such as employment, ability to drive, and relationships deserve consideration as well. The two RCTs cited at the start of the previous paragraph did not find a difference in employment status between medical and surgical groups [82, 177]. Increased likelihood of being able to drive is reported in 7–65% (median, 48%) of patients, and this is directly dependent on a seizure-free outcome [173, 180]. It remains unclear whether temporal or extratemporal epilepsy surgery patients have better overall psychosocial outcome [180].

Independent of psychiatric illness, approaching major surgery is daunting for anyone and requires adapting to a range of peri- and postoperative changes. For instance, people with epilepsy often adopt a sense of learned helplessness and develop a high degree of interpersonal dependency; it is common for these patients to retain this dependent role after surgery despite good epilepsy outcome [181]. Other patients may overestimate new possibilities and expect unrealistic life changes, like opportunities for partners that are more favorable or professional standing. The family plays an important role in the adaptation process as well. Family members may continue to be overprotective, even when the patient wants to expand his role in the family affairs (e.g., financial decisions), or to pressure the patient to fulfill expectations of now being healthy (burden of normality). Epilepsy, despite its impairments, paradoxically can provide social and emotional protection from day-to-day responsibilities and expectations [166, 182]. Particularly patients with personality disorders report disrupted family dynamics and difficulties adjusting to seizure freedom [179]. Attenuation of this type of problems can be achieved by having before and after surgery family meetings so as to identify the dynamics, the expectations from surgery, and prepare them for the impact of a life without seizures [120].

In addition, antiepileptic medications (AEDs) before or after the surgery can contribute to a range of psychiatric symptoms, from fatigue or depression to irritability and even agitation [121].

Deep Brain Stimulation

Deep brain stimulation (DBS) involves the surgical implantation of a device that delivers electrical currents to specific brain regions to modulate neurons that influence psychiatric symptoms and movement disorders. DBS surgery is reversible, and the device producing the electrical currents is adjustable. Originally approved by the FDA for essential tremor (ET) in 1997, DBS has since received FDA approval for Parkinson disease (PD) (2002) and humanitarian device exemptions (HDE) for dystonia (2003) and OCD (2009). A recent systematic review and meta-analysis of the literature assessing the effect of DBS for OCD found 18 unique studies published, describing a total of 112 patients. Although the majority of the patients improved, the interpretation of these findings was difficult due to the heterogeneity of the subjects and the variability of the target areas used to administer DBS [183]. FDA allows use of DBS for treatment-resistant OCD under a humanitarian device exemption approval. Emerging off-label indications for DBS include pain, major depressive disorder, tic disorders (including Tourette syndrome), obesity, anorexia, addictive disorders, epilepsy, pathological aggression, behavioral and psychiatric symptoms of dementia, and other movement disorders [184]. A meta-analysis of the studies assessing DBS for depression found a total of 10 studies (190 subjects), 8 of which were randomized controlled trials; the authors concluded that the evidence is promising, but at this time DBS remains an experimental treatment for depression [185].

DBS is thought to replace abnormal intrinsic activity by providing time-locked recurring stimulation that precludes pathological bursting and oscillatory activity in affected areas [186]. DBS applies an electrical current of 3–5 volts at pulse frequencies above 100 Hz [187]. At these frequencies, tissue proximate to the electrodes is depolarized and deactivated; in bordering areas, however, volume conduction leads to stimulation and propagation of action potentials remotely, activating targeted circuits [187].

The DBS unit has three main modules: a pulse generator with a battery unit (typically placed subcutaneously in the supraclavicular region), intracranial electrodes (surgically implanted), and a cable that connects the electrodes to the pulse generator (Fig. 10.1). Implantation of the DBS unit typically involves two interventions: first, with the assistance of a stereotactic head frame, neuroimaging (for precise localization) electrodes are placed in targeted brain areas. This can be done under general or local anesthesia. In order to identify the targeted brain area, microelectrodes are inserted in different areas, and the targeted areas are identified by patterns of electrophysiological activity. The electrode placement is veri-

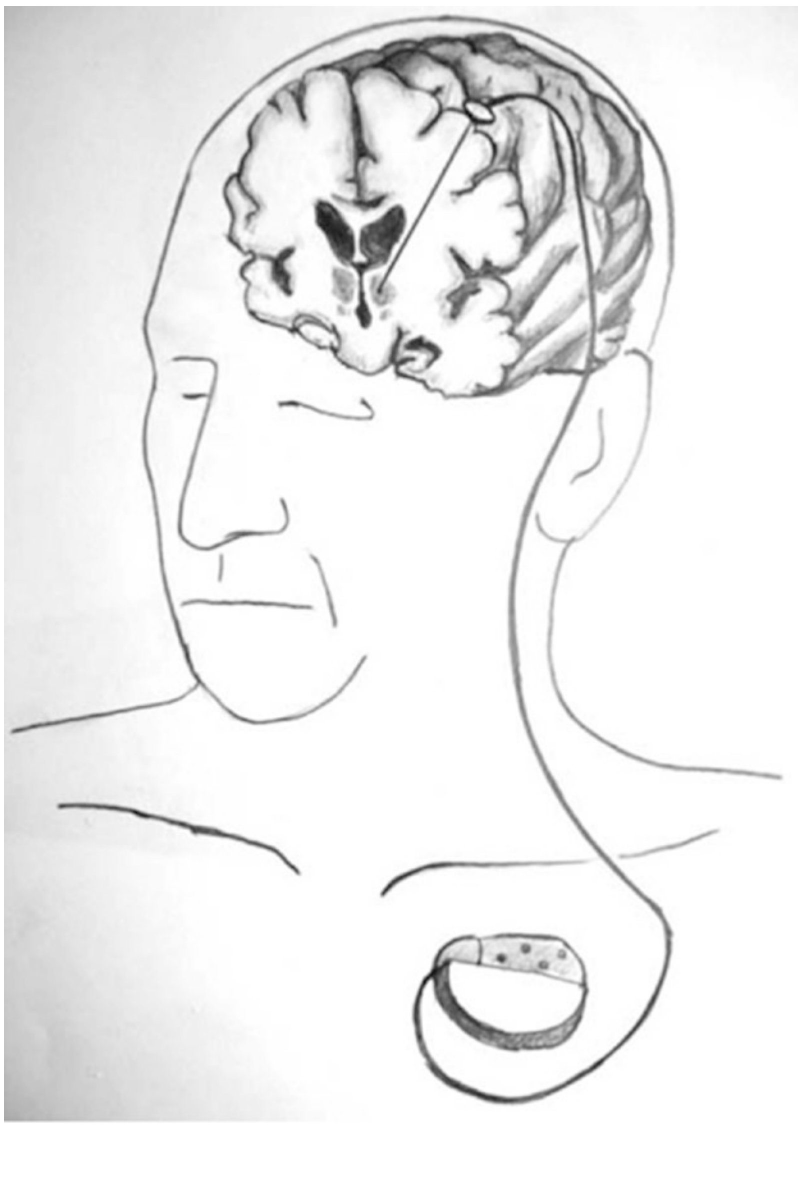

Fig. 10.1 Illustration of an implanted deep brain stimulation system [187]

fied radiographically. Improved neuroimaging techniques have shortened the duration of the intervention and have improved the precision of electrode placement [188]. A second intervention is required for placement of the pulse generator and its battery as well as to connect this unit with the intracranial electrodes. These separate interventions can be performed the same day or on different days, depending on patient's clinical condition and on logistical considerations.

Perioperative psychiatric symptoms in DBS can be related to underlying psychiatric comorbidity or to complications of the procedure. Parkinson disease (PD) is by far the most common indication for DBS; its prevalence increases with age from 0.01% (30–39 years) to 2.83% (≥90 years) [189]. In addition to its defining motor symptoms (rigidity, resting tremor, shuffling gait, bradykinesia) and autonomic dysfunction, patients with PD have a high rate of psychiatric symptoms. Up to 29% of PD patients have psychotic symptoms [190], and up to 35% have depressive symptoms with 19% meeting criteria major depressive disorder [191]. Depression in PD tends to improve over the first year after diagnosis, followed by a slow worsening of symptoms [192]. For patients with PD receiving DBS, a recent meta-analysis found a moderate change in depressive symptoms depends on the timing of the assessment following the intervention, which varies significant among studies; in general, the improvement of depression with DBS in PD tends to diminish with time [193].

The prevalence of anxiety disorders is also high in patients with PD: in one prospective study of 311 subjects, 15% of participants met diagnostic criteria for a generalized anxiety disorder, 11% for agoraphobia without panic disorder, 4% for panic disorder, and 8% for social phobia [194]. Treatment of psychosis in PD is especially challenging due to risk of increased neurological symptoms associated with most antipsychotic medications. Quetiapine [195], clozapine [196], and pimavanserin [197] have each been shown effective for treating severe mood or psychotic conditions or symptoms in patients with PD with little to no risk of worsening parkinsonian features.

In addition to the preexisting psychiatric symptoms, anxiety, agitation, and even psychosis can occur in the operating room especially when the electrode implantation is done under local anesthesia with the patient awake [198]. Possible postoperative complications include acute intracerebral hemorrhage, hematoma, edema, hydrocephalus, venous air embolism, and cerebral ischemia. Patients may also experience immediate change in mental status [199]. Postoperative confusion has been reported in up to 36% of DBS patients and hypomania in up to 15%, but these symptoms tend to resolve spontaneously [200]. Depression has been reported in up to 47.7% of patients who received DBS for movement disorders. There is no specific information about best treatment of these psychiatric presentations after DBS. Common principles of delirium management and consideration of the underlying medical disease in choosing the psychotropic medications are recommended.

Brain Tumors

Epidemiology of Brain Tumors in the USA

In 2012, an estimated 688,000 people in the USA were living with a primary brain or CNS tumor diagnosis (138,000 malignant [breast and lung most common primaries] and 550,000 benign). An estimated 69,720 new cases of primary brain tumor diagnoses were expected in 2013 including both malignant (24,620) and nonmalignant [45, 100] brain tumors. Overall, brain tumors are more common in men, and the incidence has been stable in recent years across most age groups, except in patients >85 years where they are increasing perhaps due to increased detection [201].

Psychiatric Presentations in Patients with Brain Masses

Psychiatric symptoms are common in patients with brain masses. To date, no large-scale prospective studies have systematically assessed psychiatric symptoms in patients with brain tumors. Most data are derived from case reports and case series. The reported incidence of psychiatric symptoms in brain tumors varies from 50% to 78%, and in 18% of such patients, psychiatric symptoms are the presenting clinical manifestation [202]. In 80% of patients with brain tumor and psychiatric symptoms, the tumor is located in frontal or limbic brain regions [203]. In a study of meningiomas ($n = 79$), 21% of patients presented with psychiatric symptoms in the absence of neurological symptoms [204]. Notably, meningiomas are likely to cause focal symptoms by compressing a limited region of the cortex, whereas gliomas are likely to cause diffuse symptoms. Brain tumors occur more frequently in patients with psychiatric and behavioral symptomatology. Autopsy data from patients with severe, persistent mental illness who died in mental hospitals have shown that unsuspected and undiagnosed brain tumors were more than 20 times more common in these patients than in the general population: 3% vs 0.13%, respectively [203].

Patients with brain tumors commonly have a range of psychiatric symptoms that go undetected and, as a result, untreated. For instance, the Glioma Outcome Project assessed the incidence of depression among patients with brain tumors after neurosurgery and found that depressive symptoms were reported by 15% of these patients' treating physicians and 93% of patients. Such a discrepancy highlights the possible magnitude of under diagnosis of depression in this population [205].

Although the literature suggests a tendency for left-sided tumors to cause dysphoria and depression and for right-sided tumors to cause euphoria, symptom denial, and neglect, reports of these associations between localization and corresponding symptoms have been inconsistent. Many such reports are old and predate the application of recent psychiatric and neuropsychiatric diagnostic classification systems. Nearly any type of psychiatric symptom can occur with brain tumors, and the nature of these symptoms has very little if any localizing value [206]. They may arise from structures distant from the tumor location, likely as a result of various disconnection syndromes that result from damage to or disruption of interconnecting neural pathways caused by tumors, especially those involving the corpus callosum (a phenomenon known as diaschisis). Also, the cerebral edema and mass effect that accompany brain tumors displace white matter fiber pathways. Thus, future attempts to understand the etiological relationship of various neuropsychiatric and neurocognitive symptoms to the localization of the brain tumors causing them will need to adopt more sophisticated connectivity models. Histological characteristics of brain tumors are also uncorrelated with specific psychiatric and behavioral symptoms. Extent and rapidity of tumor growth, rather than location, chiefly influence the presentation of behavioral symptoms [203].

Contributing factors that determine the type and severity of psychiatric and behavioral symptoms that co-occur with brain tumors include tumor type, rate and extent of tumor growth, and intracranial pressure. The patient's premorbid psychiatric status and history of prior psychiatric illness can also influence the psychiatric and behavioral symptoms that may occur when a brain tumor develops. In particular, an acute exacerbation of preexisting psychiatric conditions may occur due to the stress of having a terminal medical condition. The patient's premorbid cognitive ability, coping skills, and adaptive capacity, in conjunction with the adequacy and availability of psychosocial support systems, play important roles in determining the degree of dysfunction caused by tumor-associated psychiatric and behavioral complications [203].

Treatment of Brain Tumor-Associated Psychiatric and Behavioral Symptoms

Beyond general principles of managing these same clinical syndromes in any population, it should be noted that the neurologic side effects of several psychotropic medications (such as delirium and metabolic encephalopathy) may be more common in this population. Specifically, tricyclic antidepressants, low-potency typical antipsychotics, anticholinergic medications, benzodiazepines, and lithium (also a proconvulsant) are potentially deliriogenic. These agents are often best avoided; however, a previous positive response to one of these agents may warrant a very cautious trial after considering potential alternatives as well as the risks and benefits associated with these agents. The "start low, go slow" approach is especially relevant among the often medically complex population with brain tumors. Atypical antipsychotics may be preferred for their lower propensity to cause extrapyramidal symptoms, but they are not without risk of lowering the seizure threshold. In addition, providers should be mindful of potential drug–drug interactions and all the more as a patient's medication regimen becomes increasingly complex. Importantly, brain tumors are not an absolute contraindication to ECT. Unilateral brief-pulse ECT has been demonstrated to safe, effective, and well tolerated in selected patients after taking appropriate precautions.

Pharmacotherapy of Delirium in Brain Tumor Patients Non-pharmacological interventions for delirium remain the mainstay of managing the behavioral features of delirium; these include reorientation; providing a safe and supportive environment for the patient, staff, and family; family reassurance including the often transient nature of delirium (with certain exceptions); a well-lit room during the day; visible clock and calendar; familiar people, objects, and photos; early mobilization; and communicating with patient and family about the goals of care and desirable outcomes. High-potency typical neuroleptics, haloperidol, and newer atypical antipsychotics—olanzapine, risperidone, and quetiapine—may be used in low doses to target psychiatric and behavioral symptoms associated with delirium. One recent study comparing haloperidol, risperidone, olanzapine, and aripiprazole suggested similar effectiveness for improving symptoms of delirium, but they had different side effect profiles [207]. Benzodiazepines should generally be avoided in delirium management as they can worsen confusion and even occasionally cause paradoxical agitation [208].

Pharmacotherapy of Psychotic Disorders in Brain Tumor Patients Doses of antipsychotic medications in this population should generally be lower than in primary psychotic disorders. They can be often be dosed in the range of 1/10th to 1/4th of standard doses [203]. High-potency antipsychotics are more likely to cause extrapyramidal symptoms in these patients; therefore, atypical antipsychotics may be preferred due to a more favorable side effect profile.

Pharmacotherapy of Mood Disorders in Brain Tumor Patients The presence of preoperative depression has been associated with shorter duration of survival. Specifically, preoperative depression was independently associated with decreased survival in a retrospective review of more than 1000 astrocytoma patients [209]. SSRIs are widely considered first-line agents for depression and most anxiety disorders, and they are generally effective, well-tolerated, and unlikely to cause delirium (with the exception of paroxetine, which has anticholinergic activity) in this population. Methylphenidate (Ritalin) may also be effective. Its advantages include rapid onset of therapeutic activity, no effect on seizure threshold, absence of sedating or deliriogenic properties, as well was being well-tolerated [210]. Caudill et al. conducted a retrospective cohort study of the frequency and toxicity of SSRI prescription among 160 glioblastoma patients presenting to a tertiary neuro-oncology service over a 10-year period. The use of SSRIs was associated with improved survival at 2 years post diagnosis after controlling for relevant covariates. Further, SSRI prescription was not associated with significant side effects [211].

Modafinil, a non-stimulant wakefulness agent often used to treat narcolepsy, is often ideal for frail, debilitated patients who cannot tolerate the effects of psychostimulants or who cannot take stimulants for medical reasons (e.g., coronary heart disease) [212]. Commonly, a patient may be simultaneously started on a stimulant or wakefulness-promoting agent along with an antidepressant so that they benefit from the activating effect of the stimulant within days while awaiting clinical activity of the antidepressant [213].

A recent Cochrane review found no high-quality evidence on the pharmacological treatment of depression in patients with primary brain tumors. Doctors treating depressed brain tumor patients should discuss that the use of antidepressants in these patients is based on studies of otherwise healthy patients and that no high-quality clinical studies have been conducted in this population in particular. Clinicians should use best judgment considering an assessment of risks and benefits. If medication is started, patients should be followed closely to detect adverse effects and monitor effectiveness [214].

Another clinical syndrome to consider when evaluating for depression is demoralization. Demoralization has been described as a syndrome distinct from depression characterized by existential distress in patients at the end of life. People describe feelings of hopeless or helpless, often related to a loss of meaning in life. Some symptoms may overlap with major depression. Prevalence rates of demoralization in the medically ill population range from 20.6% to 33.3% [215]. Although demoralization is not a diagnosis in DSM-5, it is important to consider when addressing mood complaints in medically ill patients for potential psychotherapy referral (e.g., meaning-focused psychotherapy) [216].

Pharmacotherapy of Cognitive Impairment in Brain Tumor Patients Patient with brain tumors, often depending on location, presents with cognitive impairment. Neuropsychiatric testing can highlight deficits in memory, attention, or other cognitive domains. Multimodal treatment approaches using cognitive rehabilitation, vocational rehabilitation, and individualized pharmacotherapy are often used. Methylphenidate may reduce cognitive symptoms by improving attention and energy in adult brain tumor survivors. It has also been shown to have benefits of sustained attention over a year for childhood cancer survivors [217]. Donepezil, a cholinesterase inhibitor, has been investigated for treatment of cognitive impairment with some positive results [218]. Treatment with donepezil did not significantly improve the overall composite score (cognition), but it did result in modest improvements in several domain-specific cognitive functions, especially among patients with greater pretreatment impairments [219]. Memantine acts as an N-methyl-D-aspartate (NMDA) receptor antagonist and may have some modest clinical activity as well. The Radiation Therapy Oncology Group (RTOG) compared whole-brain radiation treatment with either memantine or placebo and found less neurocognitive decline in the memantine group [220].

Psychiatric Aspects of the Medico-Surgical Management of Brain Tumors

Management of brain tumors consists of surgical resection of the tumor, stereotactic radiosurgery, radiotherapy, and chemotherapy. Tumor removal may completely resolve psychiatric or behavioral symptoms. Otherwise, decreasing the tumor size (i.e., bulk) or halting its growth may also reduce these symptoms. Additionally, treating the acute mass effect such as increased intracranial pressure or hydrocephalus may improve cognitive functioning and decrease behavioral symptoms [221].

Cerebral edema often accompanies brain tumors, tumor progression, radiation therapy, and corticosteroid withdrawal, and it may cause headache, cognitive dysfunction, delirium, focal neurological deficits, and virtually any psychiatric symptom. Dexamethasone is the treatment of choice for cerebral edema. Many patients have improvement in their presenting psychiatric symptoms with the improvement in cerebral edema within days of initiating corticosteroid therapy.

Short-term prophylaxis with a newer-generation AED is appropriate for patients having brain surgery to prevent early postoperative seizures [222, 223]. Levetiracetam is the most common drug in use. However, it can cause behavioral side effects including irritability and impulsivity. Meta-analysis has confirmed that patients on levetiracetam have twice the relative risk of behavioral symptoms than those on placebo [224]. Lamotrigine and valproate are alternative AEDs that improve mood stability. Patients on valproate should be monitored carefully for evidence of hyperammonemia and for any of a range of potential drug–drug interactions, especially with other AEDs.

Corticosteroids

Corticosteroids are used commonly to decrease tumor-associated edema. Exogenous corticosteroids are well known to cause a range of neuropsychiatric side effects [225]. Approximately 13–62% of patients experience transient, mild-to-moderate symptoms that do not reach severity or duration criteria for psychiatric disorder [226]. These include activation symptoms, such as anxiety, insomnia, and irritability, and mood symptoms, such as dysphoria, euphoria, and lability. More serious corticosteroid-induced psychiatric disorders occur in approximately 3–6% of patients. High-dose, short-term administration is most often associated with manic spectrum disorders, whereas chronic therapy is most often associated with depression [227]. In a patient with an active corticosteroid-induced mood disorder, tapered discontinuation or reduction to minimal effective dosage is recommended, based on status of the underlying illness [228]. In a systematic review, steroid-induced manic and psychotic symptoms responded to low-dose typical antipsychotics with cessation of symptoms in 83% of patients, 60% of whom responded in less than 1 week and 80% in less than 2 weeks [229].

Chemotherapy

"Chemobrain" or cancer therapy-associated cognitive change has been identified in patients with a variety of cancers who have received chemotherapy and have experienced difficulty in executive function, multitasking, short-term memory recall, and attention [230, 231]. Up to 75% of chemotherapy patients may experience cognitive impairment [232]. Stimulants have been used clinically to combat cognitive slowing in this population, although high-quality evidence of efficacy is lacking. Similarly, evidence for the use of donepezil to treat cancer-related cognitive dysfunction remains unclear [233]. Cognitive training programs, which focus on the practice of specific skills through the use of computers, have shown some benefit in preliminary studies [233].

Radiation Treatment

External beam radiation treatment (RT) requires positioning of the patient on a flat table and immobilization with a thermoplastic mask. The table can move such that more than one beam can target tumor tissue, with the most intense radiation occurring at the intersection of the beams [234]. Stereotactic radiosurgery (SRS) focuses a high dose of radiation on one small area in the brain. SRS and stereotactic body RT can be delivered using a linear accelerator or a proprietary system, such as the CyberKnife (Accuray, Sunnyvale, CA) or Gamma Knife (Elekta, Stockholm, Sweden) [235]. In a systematic review of 93 studies of psychosocial functioning among RT patients, the median prevalence of anxiety disorders was 20%, 49%, and 17% before, during, and after treatment, respectively. The median prevalence of depression before treatment was 15%, rising to 33% during treatment, and remaining elevated at 27% after treatment [236]. Side effects of radiation treatment depend on the location, total dose, and technique. The acute side effects of brain radiation include cerebral edema for which corticosteroids can be used. Patients can develop a transient cognitive dysfunction, fatigue during treatment, and somnolence, which can persist for several months. Given the current evidence, it may be reasonable for a psychiatrist to initiate a trial of memantine, methylphenidate, or donepezil to target cognitive complaints, fatigue, and mood in this patient population. This should be done in conjunction with the patient, weighing potential risks and benefits, considering overall prognosis, and with the understanding that this would be an off-label use of the medication [237].

Pseudoprogression is transient radiographic worsening occurring up to 4 months after RT. The patient has regularly repeated scans to assess the state of the tumor, and coping with ambiguity and uncertainty is a regular challenge for the patient and family [238]. Low levels of hormones can be a late side effect of radiation therapy to the hypothalamus, pituitary gland, or thyroid [239].

These treatments are challenging for patients who have claustrophobia or anxiety about being immobilized. Several technical modifications for claustrophobic patients have been evaluated [240]. Patient education, guided imagery, meditation, and relaxation therapy may reduce distress. Also, premedication with benzodiazepines can help phobic patients tolerate the treatment. All these psychological modalities may be used in advance to reduce anticipatory anxiety and to facilitate treatment as it is being planned [238].

Take-Home Points

1. Psychiatric symptoms are very common in neurosurgical patients. They can be due to preexisting psychiatric conditions, as a direct result of the surgery or as an effect of the medical treatment used to target the underlying neurosurgical condition (e.g., chemotherapy for brain tumors).
2. Cerebral edema is a key factor in neurosurgery. Corticosteroids are widely used to treat cerebral edema due to tumor growth and are less commonly used in TBI patients.
3. Preoperative psychiatric and cognitive evaluation facilitates peri- and postoperative care by providing information about baseline mental status, coping style, psychiatric conditions, cognitive function, and prior response to psychotropic medication.

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11 Perioperative Psychiatric Problems in Organ Transplantation

Paula C. Zimbrean and Nora Proops

Introduction

Brief History of Organ Transplantation

Humankind has pursued organ transplantation as a means to heal and prolong life for millennia, with the first skin graft recorded in 3000 BC in ancient India. In biblical stories, severed ear, breast, and hand are sutured back onto the amputated figure, and in 1760 the term "transplantation" is coined, credited to the English physician John Hunter whose early experiments involved grafting rooster's spurs onto their combs. Several attempts to transplant cadaveric kidneys took place in the early 1900s, all of which failed due to immunologic rejection, a phenomenon that began to gain recognition in the 1950s. By 1954, the first solid organ, a kidney, was successfully transplanted between identical twin donor-recipients at the Brigham Hospital in Boston. The following 33 years witnessed successful transplants of the remaining solid organs: the pancreas (1966), liver (1967), heart (1968), lung (1981), and intestine (1987). The discovery of cyclosporine as immunosuppressive therapy in 1976 improved outcomes further, and in 1995 laparoscopic surgery was used for the first time to transplant a kidney, greatly reducing postoperative complications and time to recovery [1].

An exciting emerging field is the transplantation of vascularized composite allografts (VCAs)—transplantation of multiple tissues such as muscle, bone, nerve, and skin, as a functional unit (e.g. hand, face). Although the underlying illness can vary significantly, the life of patients in need for organ or VCA transplantations is marked by a significant shortage of available organs, the event of a major surgery, and the mandate of a lifelong course of immunosuppressive medications.

Organs can be harvested from deceased or living donors. Typically, more than one organ is harvested from a deceased individual, thus deceased organs comprise 80% of total donations but only 60% of all people who become donors. Up to eight solid organs (both kidneys and lungs, the liver, pancreas, intestines, and heart) can be donated from a deceased individual.

While over 130 million people in the United States are registered to become donors upon death, only 3 out of 1000 people die in such a way that supports organ transplantation. There are few exceptions to registering, including systemic cancer and infections; however, now HIV-positive individuals can donate organs to

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HIV-positive recipients. Currently, hepatitis C infection remains a barrier for donation; however, the American Society of Transplantation has issued a statement arguing for these individuals to be allowed to donate as curative treatments become more widely available. Otherwise, people of all ages and religions and regardless of citizenship status are eligible to register as donors, including those under age 18 with required parental consent. The process for deceased donation registration is straightforward; one can opt in when applying for driving licenses at the Division of Motor Vehicles or can register online directly with the Donate Life organization, which maintains the national registration list.

Organ Procurement and Allocation

Once brain death is pronounced in an individual on the registry, the process for potential organ acquisition begins. Medical representatives from the organization of organ procurement evaluate the patient; to limit conflict of interest, these medical representatives cannot be the caring physician or physician who pronounced death. Subsequently, the deceased donor's information is entered into the national allocation registry to begin the process of matching, as timing is crucial. Organs are removed surgically and transported to the recipient hospital where transplantation will take place. The deceased family is informed later which organs were transplanted and, while the recipient's information is kept confidential, further contact can be coordinated through the organization.

Legislation regarding donation has evolved over the years as the system of organ procurement and allocation has developed. The Anatomical Gift Act of 2006, enacted by 47 states by 2017 (aside from New York, Delaware, and Florida), was drafted to unify previous legislation which varied considerably between states. Firstly, it accommodated documentation commonly found on the backs of driver's licenses. More importantly, it strengthened language regarding the finality of the organ donation decision, specifically stating "there is no reason to seek consent from the donor's family because the family has no legal right to revoke the gift."

Conversely, the law also allowed an individual to sign a refusal to bar others from making a gift of the individual's parts after his or her death. The aims of this legislation were to encourage more people to register as donors and to facilitate donation proceeding after his or her death [2].

The Organ Procurement and Transplantation Network (OPTN) has developed several tools to prioritize waiting list candidates. These calculators incorporate patient- and disease-specific variables, each weighted according to relative significance, to produce a numerical value to rank candidates and determine how quickly an organ may be allocated to this individual. Here are some examples:

- For pancreatic and combined pancreatic/kidney recipients, the calculated panel reactive antibody (CPRA) calculators are used to predict organ rejection. To determine the CPRA value, a recipient's blood is tested for reactivity against potential donor HLA subtypes and then multiplied by the frequency with which those antigens are present in the population.
- For kidney transplant candidates, the estimated post-transplant survival (EPTS) index incorporates the recipient's age, time of dialysis, presence of diabetes, and history of prior transplant to estimate recipient longevity. The Kidney Donor Profile Index (KDPI) includes the deceased donor's age, ethnicity, creatinine clearance, history of hypertension, diabetes, or HCV infection, as well as cause of death and height and weight. EPTS is only considered when KDPI is less than 20%, to ensure those kidneys expected to function the longest are transplanted in recipients expected to live the longest as a way to maximize the full benefit of transplantation. [3].
- For liver transplant recipients, Model for End-Stage Liver Disease (MELD) score incorporates serum bilirubin, creatinine, and the international normalized ratio (INR) into a formula that provides a continuous variable that predicts 90-day mortality in patients with cirrhosis [4].

It is important to know that these calculators are used in conjunction with other clinical criteria to prioritize organ candidates, such as presence of comorbidities or time since dialysis inception. The treating physicians can "appeal" a patient's place on the organ waiting list for certain clinical exceptions which are organ specific. This complexity of organ allocation translates into an extraordinary level of uncertainty for the patient waiting on a decision about listing and their place on the waiting list.

Overall, slightly more than 50% of those on the waitlist receive an organ within 5 years. In 2017, 83% of the 115,757 individuals on the waiting list were for kidney transplants. When an organ becomes available, the organ procurement organization runs the match program, a national computerized system that matches donor organ characteristics against potential recipients on the waitlist. This algorithm takes several factors into account such as recipient body size, blood type, HLA compatibility, distance from donor hospital, and time on the waitlist. Notably, financial status, ethnicity, religion, and gender are not part of the match program. Based on OTPN reports, those with a liver MELD score of >35 waited on average 11 days before receiving an organ, while those with a score of 15–29 waited on average 691 days between the years of 2011 and 2014. During this period, for those waiting for a heart transplant, the average wait for AB blood type was 70 days, whereas the average wait for O blood type was 535 days [5].

For potential recipients, the criteria to be listed or to remain "active" on the waiting list vary by organ. Transplant candidates must be diagnosed with an organ disease that is suitable for transplantation and must not have any medical contraindications to transplantation, such as active malignancy or infection. The absolute and relative medical contraindications for transplantation vary by organ, are constantly evolving and, therefore, are not reviewed in this chapter. The psychiatrist or mental health clinician is often involved in this phase of evaluation and participates to the decision about listing the patient, as we will discuss below.

Despite relatively accelerated advances in surgical technique and immune suppression therapy in recent years, the need for donation remains the field's largest hurdle. In 2017, 20 people die every day while waiting for an organ, a figure that will only grow if the trend of the past decade continues. From 2005 to 2015, the waitlist grew by over 30,000, while the number of transplants performed expanded by only about 2000 [6]. As of February 11, 2018, there were 114,990 patients waiting for a solid organ in the United States, and the waitlist continues to grow, with one transplant candidate being added to the waitlist every 10 min. It is estimated that between 10% and 18% of candidates waitlisted will not survive until transplantation [7].

Adapting to Pre- and Post-transplant Life

In order to assess and assist with mental health problems during the transplantation process, it is important that the psychiatrist become familiar with the challenges patients face pre- and post-transplantation. The process starts with receiving a diagnosis of advanced, usually irreversible, organ disease. This can happen acutely, such as in postpartum heart failure or acute liver failure, or chronically, after undergoing years of treatment for diabetes-induced kidney disease. Usually a period of illness and disability precedes the referral for transplantation evaluation. The pre-transplant evaluation consists of multiple appointments with medical providers and medical tests, some of which are invasive. This phase is marked by the anxiety of being accepted onto the waiting list. Once "listed," the patient and his or her family must face the decline of his or her health status and the uncertainty of receiving an organ. Medical events can also occur in the interim, which can lead to the patient becoming ineligible for transplantation, either temporarily or permanently. Financial burden and significant shifts in social role may occur at any point in the pre- or post-transplantation period.

After transplantation, there is a period of euphoria linked to surviving the wait and the surgery and excitement about life possibilities that lie ahead. The challenges of recovery including post-transplantation immunosuppressant treatment may lead to readjustments of the patient's expectations. The experience of recovery and perisurgical care may be seen as traumatic events and lead to persistent anxiety and avoidance. In the long term, patients face the challenge of needing lifelong immunosuppressant medications. Quality of life (QOL), although markedly improved after transplantation, does not always restore to pre-illness levels. Patient may need to adjust to new physical limitations that lead to changes in their social or occupational roles. Additionally, the financial burden of post-transplant care may be significant.

Prior to transplantation, patients with organ failure may require treatment with assisted devices to compensate for the malfunctioning organ. The most common of such devices are dialysis (hemo and peritoneal), continuous venovenous hemofiltration (CVVH, a short-term type of dialysis used in the intensive care unit), *extracorporeal membrane oxygenation* (ECMO, an external technique of providing both cardiac and respiratory support), and ventricular assist devices (VADs, implantable devices used in patients with heart failure to provide adequate systemic blood flow). Initially aimed to be a bridge to heart transplantation, VADs have advanced significantly over the past two decades and have become smaller, easier to use, and more durable and have increasingly become destination therapy for patients who do not progress toward transplantation.

In this context, defining the perioperative period for organ transplant recipients can be challenging. Most pre-existing medical or psychiatric conditions are relevant for the post-transplantation course. In the majority of cases, transplant recipients are never "cured." This chapter focuses on psychiatric conditions beginning with the evaluation for transplantation and extending 1 year after the surgery. Psychiatric aspects of living organ donors will be discussed in a subsequent section of this chapter. Psychiatric aspects of VCAs are discussed in Chap. 8.

The Mental Health Evaluation of Organ Transplant Candidates

The first concerns about the psychiatric status of transplant recipients were raised very early in the history of transplantation: in 1969, "transplant psychosis" was described as disorganized speech and behavior within days post-transplantation. This syndrome was believed to be the result of an immunologic response of the body to the graft [8]. Later, it became apparent that patients' mental status and coping skills are essential for their ability to adhere to the complex post-transplant regimen. Over the years, the United Network for Organ Sharing (UNOS) acknowledged that "mental health and social support services are essential for the total care of transplant recipients, living donors, and their families" and currently requires that such services be made available [9]. Psychiatrists are often involved in the psychosocial evaluation of transplant candidates and donors and participate in the candidates' selection. The psychosocial evaluation for transplantation typically involves a multidisciplinary team that may include a psychiatrist or psychologist as well as social workers and addiction counselors. Many transplantation centers utilize a stepped care approach, with all transplant candidates and donors being evaluated by a social worker initially, who refers for a more detailed psychiatric or psychological evaluation as necessary. The goals of the psychiatric evaluation are:

1. Diagnose psychiatric disorders and identify treatment options, while considering the interference of the underlying medical problems.
2. Evaluate the patient's ability to provide informed consent about transplantation.
3. Assess the patient's ability and motivation to participate in pre- and post-transplantation medical care to ensure a good outcome.

As of 2018, there are no formal guidelines regarding absolute or relative psychiatric contraindications to transplantation listing. For patients with addictive disorders, most centers follow the "6-month rule," which requires patients to have a minimum of 6 months of abstinence before listing [10]. Poor adherence with medical treatment or substance use without a diagnosis of addiction is sometimes considered a "high-risk behavior" and may be considered a contraindication to listing in the absence of a formal psychiatric diagnosis [11]. Surveys of transplant program practices have shown that most centers consider psychotic disorders, such as schizophrenia, an absolute contraindication to transplant listing [12]. These practices are being challenged by recent reports describing patients with recent alcohol use or history of recurrent psychosis who can do well post-transplantation [13–15].

In an attempt to standardize the psychosocial evaluation of transplant candidates and to quantify predictors of psychosocial risk factors, several psychosocial risk assessment tools have been developed. The most commonly used are the Transplant Evaluation Rating Scale (TERS) [16], the Psychosocial Assessment of Candidates for Transplantation (PACT) [17], and the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) [18]. The predictive value of these instruments remains to be determined.

Because a psychiatric evaluation may ultimately exclude a patient from being "listed," the psychiatrist may find him or herself in a "gatekeeper" role, with the primary scope of practice being that of keeping high-risk patients away from the transplantation list. However, it is important to emphasize the advocacy role held by the psychiatrist evaluating transplant candidates. In addition to providing psychiatric diagnosis and treatment recommendations, the mental health evaluation of the transplant candidate offers a great opportunity to educate both patient and family about the psychiatric illness and its possible impact upon general health. The psychiatrist can also inform the transplantation team about relevant aspects of the patient's psychiatric diagnosis and treatment. Moreover, when the patient is receiving mental health care outside the main medical center, the transplant psychiatrist can play a key role in enhancing communication between the transplant team and the patient's outpatient mental health providers. To reach these goals, the psychiatrist must be familiar with the process of transplantation from the evaluation up to listing and to post-transplantation care. Ideally, the psychiatrist is embedded with the transplantation service and can join multidisciplinary meetings in which all aspects of the patient's medical care are discussed.

Psychiatric Illness in Transplant Candidates

The factors that influence mental health in transplant patients are different in the pre- and post-transplantation phase. Transplant-eligible patients have a high prevalence of psychiatric illness long before they develop organ failure and become transplant candidates. For instance, patients with hepatitis C have a 1.4–5 times higher prevalence of depression compared to the general population [19]. For transplant candidates, the pre-transplant course is marked by a chronic irreversible medical condition, which may cause psychiatric symptoms directly (e.g., hepatic encephalopathy) or indirectly by impacting physical and social functioning, including financial status and family dynamics. Post-transplant medical care incurs costs in terms of time, finances, and changes in social roles that may also contribute to developing anxiety and depression. For instance, lower perceived control has been shown to predict depression and anxiety in heart transplant recipients, particularly among women [20].

Estimating the prevalence of psychiatric illness in transplant patients is difficult. Since the psychiatric evaluation is often taken into consideration for the decision to list or not list a candidate, many patients may minimize their problems in order to increase their chances of being listed. The psychiatric assessment can be obscured by symptoms of underlying medical illness such as fatigue, cognitive problems, or psychomotor retardation. In extreme cases, such as the evaluation of a comatose patient in liver failure, the interview may not even be possible and the evaluation is made based exclusively on chart review and interviewing family members. Structured instruments such as psychiatric scales may be used to bypass these difficulties, but very few have been validated in transplant patients. Moreover, validation studies have been limited to specific groups; for instance, the PHQ appears to be a valid instrument for depression in dialysis patients [21].

Depression and Anxiety A recent systematic review of 22 studies, which included 3055 liver transplant candidates, showed a median prevalence of depression of 24%, significantly higher than in the general population. Up to 80% of liver transplantation patients report depression in the period preceding transplantation. This wide range was likely due to the variety of instruments used to assess depression but also to the differences in the populations studied, in terms of severity and cause of liver disease [22]. The prevalence of major depressive disorder in lung and heart transplant recipients was 25.5% [23]. In a cross-sectional study of 200 kidney transplant patients, 75% had depression [24]. Anxiety also has a high prevalence in organ transplant patients: 28.7% in liver transplant recipients [25] and 50% in kidney transplant patients [24].

Substance Use Disorders 64% of heart transplant candidates reported a history of a substance use disorder, with tobacco use disorder being the most prevalent (61.4%) [26]. Among lung transplant candidates, 21% used alcohol at the time of the pre-transplant evaluation [27]. An "anonymous" toxicology study in liver transplant candidates found that 20% of patients tested positive for alcohol, while 30% tested positive for either alcohol or illicit substances, and only 4% had reported their use [28]. For patients on hemodialysis, depression is less common in transplant candidates, compared to patients now waiting for a transplant [29]. Most guidelines consider active substance use a contraindication to transplantation; however, guidelines do not specify details such as the duration of abstinence required or how abstinence should be monitored.

Cognitive Impairment (CI) and Delirium CI is common among patients with end-stage organ disease and may be caused directly by the malfunction of that particular organ (e.g., hepatic encephalopathy or uremia) or may be related to medical comorbidities (such as diabetes frequently associated with end-stage kidney disease). Lung transplant candidates report a high prevalence of organic brain syndrome (19% pre-transplantation and 50% post-transplantation) [30]. Close to 50% of liver transplant candidates experience CI in the form of overt hepatic encephalopathy [31]. CI is frequent in patients with chronic kidney disease, with memory difficulties being the domain most commonly affected [32].

Sleep Disturbances Poor sleep quality is reported by almost half of liver and heart transplant candidates [33]. Before transplantation, sleep is significantly impacted by physical symptoms, such as nycturia, pruritus, or pain. Obstructive sleep apnea [34] and restless legs syndrome [35] are present in almost a fourth of patients with chronic kidney disease, even in early stages.

Other Conditions Although anecdotal evidence and clinical common sense suggest personality disorders are significant risk factors for poor outcomes after transplantation, there is remarkably little literature about the prevalence of personality disorders in the transplant population; a cross-sectional study of cardiothoracic transplant recipients showed that 33% of them met criteria for personality disorders [36].

Psychiatric Presentations in Organ Recipients

Delirium and Cognitive Impairment A recent study of 181 liver transplant recipients reported that 21% of them developed delirium. In this group, a history of encephalopathy that required hospitalization and pre-transplant antidepressant use were associated with a higher risk of delirium [37]. Rapid correction of hyponatremia ($\Delta Na \geq 12$ mmol/L/24 h) is another risk factor for delirium in liver transplant recipients [38]. A prospective study of lung transplant patients found a 37% incidence of delirium within the first week post-transplantation [39, 40]. In kidney transplant recipients, delirium has been reported but it is rare. It is believed that cognitive function improves after kidney transplantation for previously dialysis-dependent patients; however, the clinical implications of this change still need to be explored [41].

Psychiatric side effects of immunosuppressant medications are summarized in Table 11.1.

Among the immunosuppressant therapies used post-transplant, glucocorticoids are commonly prescribed and associated with psychiatric side effects. However, in most patients, these are mild and reversible. Severe manifestations such as mania, psychosis, and depression rarely occur below doses of 40 mg/day and reach an incidence of 18% at doses exceeding 80 mg/day with mania being the most common [43]. A retrospective review in the UK compared patients taking glucocorticoids to those with the same underlying disease not taking glucocorticoids and found that glucocorticoid exposure was associated with a hazard ratio of 6.89 for suicide or suicide attempt, 5.14 for delirium, 4.35 for mania, and 1.83 for depression [44]. Patients are more likely to exhibit manic symptoms with acute therapy and depressive symptoms with longer-term therapy exceeding 6 months [45]. Older patients are more vulnerable to developing delirium and cognitive deficits. Memory impairment may be seen only 3 months into therapy, after controlling for inattention, affective disturbance, generalized global cognitive decline, or severity of disease [46]. For patients with steroid-induced psychosis, Davis et al. found that low-dose antipsychotics led to resolution in 83% of patients with the majority occurring within 2 weeks (33% in 3 days, 60% 1 week, and 80% in 2 weeks) [47].

Sleep Disturbances Studies suggest that sleep tends to improve after transplantation compared to the pre-transplant period [33], yet up to 50% of liver recipients and 49% of heart recipients continue to report poor quality of sleep [33]. Sleep tends to improve in liver transplant recipients with alcoholic liver disease but not in those with hepatitis C [48]. In a cohort of 142 dialysis patients who received kidney transplantation, 46% experienced a clinically relevant improvement in overall sleep quality, while 21% experienced a clinically relevant deterioration [49]. In lung transplant recipients, the prevalence of obstructive and central sleep apnea was 42.9% and 6.5%, respectively [50].

Posttraumatic Stress Disorder (PTSD) The experience of being ill, the long evaluation and wait leading to transplantation, as well as the surgery and the early recovery, can be experienced as traumatic and thereby contribute to transplant-related PTSD (PTSD-T). In some cases, the prevalence for psychiatric illness is higher in the early post-transplantation phase. A study of lung and heart recipients found that 14% and 15%, respectively, experienced PTSD-T, most within the first-year post-transplant. [51]. Risk factors for developing PTSD-T include prior psychopathology, greater ICU benzodiazepine use, and psychotic symptoms in the ICU [52]. For liver transplant patients, PTSD-T tends to be more common in the first 2 years after liver transplantation [25]. Among lung and heart transplant recipients, 38.3% reported psychiatric disturbances, 25.5% of which had major depressive disorder and 17% PTSD-T [23].

Adherence with treatment is complex and of utmost importance in the transplantation world. Adherence may include behaviors such as medication adherence, regular exercise, abstinence from use of harmful substances, attendance at scheduled clinic visits, lack of pet keeping, or adherence to dietary recommendations. Multiple studies have associated good adherence with higher graft survival [53–55]. A recent study of heart transplant recipients reported that only 72% of respondents were taking their medications correctly and only 58% exercised at least weekly [56]. Risk factors for nonadherence include younger age, poor social support, financial hardship [57], and psychiatric conditions such as depression and anxiety [58]. Psychiatric illness is not uniformly a risk factor for nonadherence [57]. In fact, patients with serious mental illness may have good adherence after transplantation, especially if they receive close psychiatric follow-up [15]. A recent systematic review concluded that there is no one particular

Table 11.1 Psychiatric considerations of common immunosuppressive medications [42]

Psychiatric side effects	Drug-drug interactions	Levels monitored	Diabetes	QTc prolongation	Hyponatremia	Leukopenia	Increased lipids	Seizures
Cyclosporin (Neoral) Mechanism: inhibition of production and release of interleukin-2								
Catatonia Mania Depression Psychosis Encephalopathy	Lowers seizure threshold (synergistic effect with *bupropion*) *Donepezil, fluvoxamine, and vilazodone* may increase cyclosporine levels May increase bioavailability and effects of *alprazolam* *Modafinil* may diminish cyclosporine effectiveness Low cholesterol increases risk of neurotoxicity by allowing greater CNS penetration	Yes	<2%	Not reported	Not reported	<6%	Not reported	1–5%
Everolimus (Afinitor, Zortres) Mechanism: prevents protein synthesis and cell proliferation through phosphorylation of P70 S6 ribosomal protein kinase; does not affect calcineurin activity								
Psychiatric symptoms (21%, including anxiety, aggression, agitation, panic attacks, abnormal behavior, and obsessive compulsive disorder) Insomnia (17%)	Concurrent use of *carbamazepine* (or other CYP 3A inducer) may decrease *everolimus* levels Concurrent use of *nefazodone* (CYP 3A substrate) may increase *everolimus* levels	Yes	1–32% (liver transplant) 1–10% kidney transplant	Not reported	Not reported	Transplant, 3–12% [25]	Kidney transplant, 21% [38]; liver transplant, 24% [25]	5%
Mycophenolate mofetil (CellCept) Mechanism: inhibits proliferative responses of T and B lymphocytes								
Anxiety, asthenia (35–43%) Insomnia (40–52%)		No	No	Not reported	Not reported	<11%	Not reported	Not reported

Prednisone Mechanism: induces lipocortin (an anti-inflammatory protein which inhibits the enzyme phospholipase A2 which furthermore inhibits synthesis of prostaglandins and lipoxygenase products)								
Mania, depression, psychosis, anxiety More frequent at doses above 40 mg/day Up to 50% of patients have some psychiatric symptoms Typically resolve within 6 weeks of discontinuation	May reduce the *clozapine* plasma concentration due to weak-to-moderate CYP1A2 or CYP3A4 induction Decreases *donepezil* and *mirtazapine* concentrations	No	Hyperglycemia: odds ratio 1.77 for doses up to 40 mg/day HC 10.34 for 120 mg HC/day	Not reported	Not reported	Not reported	Not reported	Not reported
Sirolimus (Rapamune) Mechanism: inhibits cytokine (Interleukin (IL)-2, IL-4, and IL-15) stimulated T lymphocyte activation and proliferation; inhibits antibody production								
Posterior reversible encephalopathy syndrome (PRES) Progressive multifocal leukoencephalopathy (PML)	*Vilazodone* may increase sirolimus level	Yes	3–20%	Not reported	Not reported	3–20%	<90%	Not reported
Tacrolimus (PROGRAF) Mechanism: inhibition of T-lymphocyte activation, proliferation and T-helper-cell-dependent B-cell response								
Insomnia (9–64%) Fatigue (2–16%) Catatonia **Posterior reversible encephalopathy syndrome (PRES)**	*Carbamazepine, oxcarbamazepine*, and *modafinil* (3A4 inducers) decrease tacrolimus trough concentrations and may increase risk of organ rejection *Phenobarbital* (3A4 inhibitor) decreases tacrolimus effect	Yes	10–37%	Reported; *Caution with all QTc-prolonging psychotropics*	<15%	13–48%	7–34%	<15%

HC hydrocortisone

intervention that improves adherence in organ transplant recipients [59]. Despite standardized pre-transplant education, the beliefs about the usefulness of immunosuppressive medications vary significantly [60]. Therefore, the treatment plan for transplant recipients with poor adherence must be individualized and should address all relevant barriers to care including financial concerns, social factors, psychological schemas, and psychiatric disorders.

Some psychiatric disorders may even improve with overall physical recovery post-transplantation. A cross-sectional study of 1067 kidney transplant recipients showed that the prevalence of depression in kidney recipients post-transplantation was much lower (22% versus 33%) than in patients on hemodialysis awaiting transplantation [61]. These results have been challenged, though, by a recent prospective study of the psychiatric impairments in kidney transplantation (PI-KT study), which showed similar prevalence of depression and anxiety pre- and post-transplantation [62]. Neurocognitive disorder appears to worsen after lung transplantation [63] but improves with kidney transplantation [64].

Other psychiatric conditions may appear later during post-transplant follow-up. For heart transplant recipients, depression has been described more commonly in the first 2 years post-transplantation [65]. Some patients may be at risk for developing depression even more than 10 years after transplantation: one study reported that 37% of young patients having depression more than 10 years post heart transplant [66]. A review of 54 studies found a rate of alcohol relapse at 0.003 cases per year for lung or heart/lung, 0.014 for kidney, 0.045 for liver, and 0.049 for heart recipients. The incidence of illicit drug use is lower: 0.009 cases per year overall (kidney 0.01, heart 0.014, and liver 0.002 cases/year) [67]. In general, relapse to substance use tends to occur later post-transplantation. Only one-third of alcohol relapses after liver transplantation occur in the first 2 years. A recent report of 712 patients who had received liver transplants for alcoholic cirrhosis were followed for an average of 9 years and showed a relapse rate of alcohol use with recurrent alcohol cirrhosis of 18% [68].

Impact of Psychiatric Disease Upon Quality of Life and Transplant Outcomes

Many studies have assessed how psychiatric disease may impact the medical and psychosocial outcomes after organ transplantation (Table 11.2).

Delirium post-transplantation is associated with increased hospital stay [37, 39]. Overall, depression is associated with a lower quality of life (QOL) post-transplantation [70] but also with an increased risk of graft failure [105] and increased mortality pre- and post-transplantation [104, 107]. Treating depression may help mitigate these risks [95, 96]. In fact, depression does not always lead to nonadherence [84, 97]. It appears that mental health needs in general, regardless of the psychiatric diagnosis, tend to associate with increased risk of poor adherence with immunosuppressant treatment [89]. For patients with alcohol dependence, complete abstinence from alcohol for life post-transplant is expected before one can be considered for transplantation; however, it is not clear what amount of post-transplant alcohol use significantly influences post-transplant outcomes [80].

This body of literature has significant limitations. The post-transplant outcomes can be influenced by the multiple medical conditions these patients have and also by surgical factors such as the quality of the graft or the "cold time" (the time between procurement and transplantation). There are very few prospective studies with sufficient statistical power to address these confounders when studying the impact of psychiatric disease. In addition, due to the established necessity of patient selection driven by the shortage of organs, there is very limited information on patients considered to have high psychosocial risk, since those patients rarely receive an organ. A recent systematic review of the evidence of pre-transplant mental health findings upon post-transplantation outcomes concluded that more information is necessary to test these factors as generalizable predictors of post-transplant outcomes [108].

Table 11.2 Impact of psychiatric problems on medical outcomes and quality of life in organ transplant recipients

Study	Study type	Population	*N*	Measure	Outcome and comments
Baguelin-Pinaud (2009) [69]	Cross-sectional	Kidney recipients	60	HADS MINI	Depression and anxiety correlated with quality of life
Baranyi (2013) [70]	Retrospective	Kidney, heart, liver recipients	123	SCL-90-R SF36	Psychological symptoms associated with lower QOL
Burkhalter (2014) [71]	Cross-sectional	Kidney recipients	926	ESS	Increased daytime sleepiness associated with non-adherence
Calia (2011) [72]	Cross-sectional	Liver candidates	44	CBA 2.0	Preoperative fear predicted acute rejection
Calia (2011) [72]	Cross-sectional	Kidney recipients	33	CBA 2.0	High psychoticism scores predicted graft rejection
Chacko (1997) [73]	Prospective	Heart candidates	94	CA MMSE BDI PAIQ MCMI	Interview-determined ratings of social support and pre-transplant adherence with treatment regimen were also potential predictors for survival Clinical impression of "high" psychosocial risk was associated with increased mortality relative to "low" risk
Corruble (2011) [74]	Prospective	Liver and kidney candidates	339	BDI	Pre-transplant depression associated with 3–4 times increased risk of graft failure post-transplant
Cukor (2009) [75]	Cross-sectional control group: patients on hemodialysis	Kidney transplant	94	BDI ITAS	Higher level of depression correlated with missed medications
Davydow (2015) [52]	Review	Organ transplantation	738	Multiple	Posttraumatic stress symptoms consistent with worse QOL
Dobbels (2008) [76]	Retrospective observational	Kidney recipients	47,899	MC	Depression associated with higher mortality
Dobbels (2009) [77]	Cross-sectional	Kidney-adolescents	23	BDI Kids screen	75% of depressed patients had difficulty with adherence
Errichello (2014) [78]	Cross-sectional	Liver recipients	51	MINI SF36 SSA SSI	Major depressive disorder was associated with higher risk of rejection, major depressive disorder or presence of two psychiatric diagnosis was associated with lower adherence
Favaro (2011) [79]	Cross-sectional	Heart recipients	207	SCID	Major depressive disorder was an independent risk factor for malignancy
Grat (2014) [80]	Retrospective	Liver recipients	432	CA	Mortality in alcoholic liver disease was independent from alcohol use post-transplant
Guimaro (2011) [81]	Cross-sectional	Acute liver failure	24	SF36 HADS BDI IES	Anxiety and depression negatively correlated with QOL
Havik (2007) [82]	Prospective	Heart recipients	147	BDI	Depressive symptoms associated with increased risk of mortality
Jin (2012) [83]	Cross-sectional	Liver recipients	92	PTSD-SS	Worse QOL if PTSD was present

(continued)

Table 11.2 (continued)

Study	Study type	Population	*N*	Measure	Outcome and comments
Jindal (2009) [84]	Retrospective	Kidney recipients	32,757	MC	Depression associated with nonadherence
Jowsey (2012) [85]	Prospective	Heart recipients	68	MMPI	Optimists had higher QOL
Snipelisky (2015) [86]	Retrospective	LVAD	136	PHQ-9	Depression was associated with increased risk of re-hospitalization
Kugler (2014) [87]	Cross-sectional	Heart recipients	203	SF36	Depression associated with lower QOL
Kusleikaite (2007) [88]	Cross-sectional	Kidney recipients	61	BDI SF36	Depression correlated with lower QOL
Lamba (2012) [89]	Cross-sectional	Liver recipients	281	Questionnaire	Mental health needs associated with nonadherence
Madan (2012) [90]	Prospective	Heart candidates	96	MCMI	Depression associated with greater mortality independent of heart disease duration
Novak (2010) [91]	Prospective	Kidney recipients	840	CES-D	Mortality higher in patients with depression
Owen (2006) [92]	Retrospective	Heart recipients	108	CA	Prior suicide attempt: increased risk of infection (RR 13.8) Prior psychiatric hospitalization: increased risk of death, infection, subsequent hospitalization History of drug use: increased risk of death, infection, hospitalization
Rice (2013) [93]	Retrospective chart review	Liver recipients	300	CA	Alcohol use post-transplant correlated with decreased graft survival and increased allograft fibrosis
Rodrigue (2013) [94]	Cross-sectional	Liver recipients	236	Phone questionnaire CA	Pre-transplant mood disorder associated with nonadherence
Rogal (2011) [95]	Prospective	Liver recipients	179	BDI	Depression post-transplant not found to be associated with medical outcomes Patients with depression on antidepressants had less rejection than patients with depression not taking antidepressants
Rogal (2013) [96]	Prospective	Liver recipients	167	BDI	Untreated depression associated with long-term mortality independent of hepatitis C
Russel (2010) [97]	Cross-sectional	Kidney transplant older than 55	37	BDI	Depression not found to predict adherence
Shapiro (1995) [98]	Prospective	Heart candidates	125	CA	Psychosocial risk associated with number of rejection episodes Nonadherence associated with substance abuse history, personality disorder, living arrangements, and global psychosocial risk

Table 11.2 (continued)

Study	Study type	Population	*N*	Measure	Outcome and comments
Sharma (2013) [99]	Retrospective	Heart recipients	31	DS 14	Type D personality associated with increased mortality and early allograft rejection
Sirri (2010) [100]	Prospective	Heart transplant	95	SCID	Hostility associated with lower rate of survival
Smith (2014) [101]	Prospective	Lung transplant	201	BDI-II	Cognitive impairment increased mortality Depression at 3 months post-transplant associated with greater mortality
Smith (2017) [102]	Prospective	Lung transplant	49	Neurocognitive assessment battery[a]	Better neurocognition was associated with longer survival (hazard ratio [HR] = 0.49 [0.25–0.96]) Declines in executive function tended to be predictive of worse survival.
Smith (2017) [103]	Prospective	Lung recipients	273	BDI-II PSSS	Higher depressive symptoms and lower social support were associated with greater mortality only among individuals with longer LOS
Spaderna (2010) [104]	Prospective	Heart candidates	318	CA	Depression associated with increased mortality
Tsunoda (2010) [105]	Retrospective	Kidney recipients	116	ZSDS	Depression associated with increased risk of rejection
Weng (2013) [106]	Cross-sectional	Kidney recipients	252	ITAS depression	Depression not found to be associated with nonadherence

CA clinical assessment, *CES-D* Center for Epidemiologic Studies-Depression Scale, *DS 14* type D scale, *BDI* Beck Depression Inventory, *CBA 2* Cognitive Behavioral Assessment 2.0, *HADS* Hospital Anxiety and Depression Scale, *IES* Impact of Event Scale, *ITAS* Immunosuppressant Therapy Adherence Scale, *MINI* Mini-International Neuropsychiatric Interview, *MMPI* Minnesota Multiphasic Personality Inventory, *MCMI* Millon Clinical Multiaxial Inventory, *MC* Medicare claims, *PAIQ* psychological adjustment to illness questionnaire, *PTSD-SS* PTSD self-rating scale, *PSSS* perceived social support scale, *QOL* quality of life, *SCID* structured clinical interview for diagnostic and statistical manual of disorders, *SF36* short form health status questionnaire, *SCL-90-R* Symptom Checklist-90-Revised, *SSA* Siegle Scale for Adherence, *SSI* Scale for Suicidal Ideation, *ZSDS* Zung Self-Rating Depression Scale

[a]Neurocognitive battery included: assessment of executive function (Trail Making Test, Stroop, Digit Span), processing speed (Ruff 2 and 7 Test, Digit Symbol Substitution Test), and verbal memory (Verbal Paired Associates, Logical Memory, Animal Naming, and Controlled Oral Word Association Test)

Psychiatric Treatment of Transplant Candidates and Recipients

Pre-transplant

It is general practice to encourage and at times stipulate as a prerequisite for acceptance to transplant listing that the patient is in mental health treatment, if deemed necessary. The mental health treatment of organ transplant candidates poses significant challenges. First, some medications may be contraindicated due to their potential for organ toxicity (e.g., lithium in patients with chronic kidney disease), drug-drug interactions (e.g., typical antipsychotics may increase the risk of QTc prolongation in association with ondansetron, frequently used for nausea), or risk of worsening an already compromised physical status via side effects (e.g., sedation with mirtazapine) [109]. Frequent medical hospitalizations and clinic visits, as well as cognitive impairment, may preclude patients from participation in formal mental health care. For patients with severe psychiatric symptoms who require inpatient care, psychiatric or addiction units may not be equipped to address their medical needs. Such patients may be treated on a medical unit with close collaboration by the consultation psychiatrist or counselor. Often, patients live far from transplant centers or from mental health facilities; for these patients, delivering psychotherapeutic interventions over the phone may prove a viable option [110, 111].

Post-transplant

Immediately post-operatively, mental health clinicians are often asked to assist with the diagnosis and management of delirium. Post-transplantation delirium is approached by a systematic evaluation of risk factors and potential causes, which are discussed in detail in Chap. 4. Identifying and treating the acute medical conditions contributing to delirium (e.g., infection and metabolic disturbances), simplification of medication regimen if possible (e.g., reducing opioids or benzodiazepines), and behavioral interventions (e.g., promoting access to daylight, frequent reorientation, normalization of sleep-wake cycle, and early mobilization) are essential for recovery from delirium. For agitated delirium, antipsychotic medications remain the first line of treatment. Antipsychotics can be safely used for the treatment of delirium or for steroid-induced psychosis in the post-transplant phase while monitoring carefully for elevated QTc, seizures, hyponatremia, and neutropenia.

Psychotherapy plays an important role in post-transplant care and is often the first line of treatment due to the increased risks of medication use in this vulnerable population. Common themes that can be the focus of psychotherapy early post-transplantation include medication adherence [112], living with an increased risk of health problems compared to the general population (malignancies, infections), expressing gratitude toward the donor or their family, coping with loss of time spent waiting for an organ, loss of social status, loss of financial situation [113, 114], changes in social role, coping with post-transplant physical limitations, feelings of guilt, and, finally, body image concerns [115]. Many transplantation centers offer specific counseling focused on coping with transplantation such as interventions for medication adherence or to help communicate with the donor or the donor's family.

Living Organ Donors: Psychiatric Assessment and Management

In the context of organ shortage, living organ donation is increasing and mental health clinicians are often asked to evaluate potential living organ donors. As of March 2018, the following organs or parts of organs can be donated by living donors: the kidney and liver lobe more commonly. The uterus, lung, intestine, or pancreas can also be donated, but donation of these organs occurs less frequently. For living donation, a healthy person undergoes surgery for the benefit of someone else. There are three main types of living organ donation. The first is directed donation in which the donor specifically names the person to whom they are donating. This is the most common type of living donation. In a directed donation, the donor may be a biological relative (e.g., a parent, sibling, adult child), a biologically unrelated person who has a personal or social connection with the transplant candidate (e.g., spouse, friend), or a biologically unrelated person who has heard about the transplant candidate's need (e.g., through church or social media). The second is nondirected/altruistic donation in which the living donor donates to a center that coordinates the match to the recipient in need. Throughout the process, the donor may meet the recipient or not, based on the patient's preference and the center's policy. The third type of donation is paired donation, which occurs when several donor-recipient pairs who are immunologically incompatible are "matched" so that each recipient receives an organ.

Standards for the living donor are more stringent considering the increased medical risk involved. Consenting adults are eligible and must be physically healthy, including no history of chronic medical conditions or organ-specific conditions that may worsen with the donation. Individuals should have strong social supports and have stable psychiatric conditions—namely, that individuals are not deemed to be high risk for suicide. Contraindications also include high suspicion for donor coercion or illegal financial exchange between donor and recipient. To be eligible for kidney donation, donors may not have a history of uncontrolled hypertension, hypertension with end-organ damage, or diabetes. For liver donation specifically, exclusion criteria include testing positive for HCV RNA, HBsAg, or alpha-1-antitrypsin subtypes, in addition to prior liver donor or with expected donor remnant volume less than 30% of native liver volume [116].

The donor mental health evaluation is similar in content to a pre-transplant candidate evaluation. In addition to determining the presence of a psychiatric disorder and the need for treatment, the donor evaluation places a greater emphasis on the ability to give informed consent and determining whether there is coercion, psychological pressure, or unhealthy motivations driving the desire to donate (e.g., creating a relationship with recipient, financial remuneration). In most countries, including the United States, it is illegal to accept financial compensation for donating an organ; compensation for donation-related expenses (travel, utilities while in recovery) is acceptable. Due to the complexity of living donation, some ambivalence about the decision is to be expected; however, if the ambivalence is considered too intense, it may become a reason not to move forward with the surgery. As of now, there are no guidelines about absolute or relative psychiatric contraindications to organ donation. In general, if a psychiatric condition impacts one's ability to give informed consent about the surgery, that person is considered to be an unsuitable donor.

Laparoscopic and semi-robotic surgeries are relatively new techniques that have decreased the duration of surgery as well as recovery period for living donors. [117]. Some kidney donors spend as little as 3 days in the hospital after the surgery [118]. Full physical recovery is expected as major immediate postsurgical complications are rare. Mortality in kidney donors is extremely low: surgical mortality from live kidney donation was 3.1 per 10,000 donors and has not changed over the last 15 years despite differences in practice and selection [119]. Although the immediate recovery happens relatively quickly, the long-term health consequences of organ donation are not yet fully understood: 10.8% of living liver donors have delayed recovery of liver function [120]. For long-term outcomes, kidney donors appear to have a mildly increased risk of developing end-stage kidney disease compared to the general population [121]. Pancreas donors have a 10–25% risk of developing insulin-dependent diabetes after donation [122].

In general, pre-donation psychiatric problems are a risk factor for perioperative surgical complications in living kidney donors [123] and are associated with a longer length of hospital stay after surgery [118]. Pre-donation depression is associated with more pain after surgery [124]. Preoperative motivational interviewing (a type of psychotherapy focused on helping the patient to implement change) that addresses the ambivalence about donation was linked with fewer physical symptoms, lower rates of pain, and shorter recovery times at 3 months post liver donation. [125]. The validity of a standardized tool for the psychosocial evaluation of liver organ donors called the Live Donor Assessment Tool (LDAT) is currently under investigation [126].

Postoperatively, the psychiatrist may be asked to address new-onset psychiatric problems such as anxiety and cognitive impairment or to assist in pain management. As donors are healthy preoperatively, they tend to be more alert in the intensive care unit; nevertheless, their level of stress in this environment should be monitored [127]. Contrary to early accounts, organ donors report postoperative pain less intensely than anticipated [128]. Mild frontal lobe impairment and attention deficits have been found 1 week after surgery in living liver donors [129]. Psychological conflicts related to donation may become apparent in the immediate perioperative period, such as feelings of vulnerability, a need to follow the recipient's progress, and feeling a closer relationship with the recipient [130]. Since smoking in living kidney donors has been associated with worse outcomes of both donors and recipients, some kidney donors may require help with smoking cessation or maintaining abstinence in the pre- or postoperative setting [131].

Psychiatric complications such as depression tend to develop later post-donation. Cumulative frequency of depression diagnosis after kidney donation was 4.2% at 1 year and 11.5% at 5 years [132]. Non-spousal unrelated donors appear to have the highest risk for developing depression, while loss of graft of death of the recipient also plays a role [132] as does the recipient's hospitalization [133]. New-onset psychiatric conditions after living liver donation occur in 4% of donors, with depression and anxiety being the most common followed by substance misuse and conversion disorder [134]. Being without a partner, younger age, lack of social support, and an avoidant coping style pre-donation are associated with greater psychological distress in donors after kidney donation [135]. Early post-donation, as organ function is recovering, doses of psychotropic medications must be adjusted accordingly [136]. Beyond the recovery period, it is reasonable to avoid psychotropic medications with organ-specific toxicity (e.g., lithium for kidney donors), although there is no clear evidence of a higher risk for toxicity in organ donors compared to the general population.

Despite the risks described above, it is important to remember that organ donation may be associated with psychological benefits such as with moderate increases in self-esteem and psychological growth [137]. Importantly, the majority (over 85%) of donors do not regret having donated [138].

Conclusion

Organ transplant recipients and donors have complex mental health needs due to preexisting psychiatric conditions, the psychological impact of end-stage organ disease, and the many entailments of organ transplantation. Pre-transplant mental health evaluations aim to identify mental health needs to identify interventions that increase the chances of successful post-transplant outcomes. Due to the shortage of organs available, patients with psychiatric conditions or high-risk behaviors may be excluded from being listed, yet there are no formal guidelines about what constitutes proper exclusion criteria. In addition to their participation in patient selection, psychiatrists can help transplant candidates minimize the impact of psychiatric illness on their quality of life. Post-transplant mental health care must take into consideration the complexity of these patients, including medications and specific life changes with which patients must cope.

Take-Home Points

1. Due to the high prevalence and powerful impact of psychiatric and addictive disorders in transplant candidates, UNOS formally recognizes the identification and management of mental health-care needs as essential for transplant recipients as well as for organ donors.
2. The shortage of organs necessitates a system of transplant candidate selection, and psychiatrists are often involved in the multidisciplinary assessment of transplant candidacy.
3. Physical impairments and a heavy burden of health-care requirements commonly prevent transplant patients from participating in traditional mental health care.
4. Evidence suggests that untreated psychiatric conditions negatively impact post-transplant outcomes.

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12 Psychosocial Evaluation and Management of Weight Loss Surgery Patients

Raymone Shenouda

Introduction

The prevalence and severity of obesity are progressively increasing for children, adolescents, and adults [1, 2]. Obesity is associated with many health complications [3] and with an increased hazard ratio of all-cause mortality [4]. In 2013 the American Medical Association recognized obesity as a disease. While it is evident that obesity poses a significant burden on health-care economics, it is difficult to quantify this cost. One meta-analysis found that the estimate of annual medical costs of obesity per individual was $1910 ($1239–2582) in 2014 USD, accounting for $149.4 billion at the national level [5]. So far, most diets result in modest and likely short-term outcome [6, 7]. Pharmacological treatments may be used adjunctively to diet and exercise and increase weight loss by 4–6% over 1–2 years [8, 9]. Typically, this boosting effect to diet and exercise wanes, and the weight loss does not last upon discontinuation of the pharmacologic agent. Moreover, some pharmacologic therapies for weight loss have been associated with serious side effects including hypertension, arrhythmias, physiological dependence, valvular pathology, and steatorrhea.

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Given these considerations, weight loss surgery (WLS) over the past two decades has rapidly gained support as a successful and durable treatment option for severe obesity. In addition to its benefit on weight loss, WLS also appears to improve metabolic status, reduce cardiovascular comorbidities, and increase quality of life [10, 11]. Literature also suggests that bariatric surgery reduces long-term mortality associated with obesity and its comorbidities [12].

In this chapter, we summarize the currently available WLS procedures and discuss the psychosocial evaluation of patients seeking weight loss surgery. We also describe the pre- and post-operative psychosocial care to optimize the outcome of WLS patients.

Weight Loss Surgery

Eligibility and Approved Procedures

Several organizations, including the National Institute of Health, American College of Surgeons, and the American Society for Bariatric and Metabolic Surgery (ASBMS), have issued guidelines regarding the medical indications for WLS. Although those guidelines differ slightly, they tend to favor bariatric surgery for those with a BMI of >40 kg/m^2 or those with a BMI of >35 kg/m^2 with comorbidities including diabetes, hypertension, obstructive sleep apnea, congestive

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heart failure, and hyperlipidemia, [13]. About 15 million people in the USA have morbid obesity, but only 1% of the clinically eligible population is treated for morbid obesity with WLS [14]. It is imperative for the mental health provider involved in psychosocial evaluation for WLS to be familiar with the available surgeries and understand their efficacy, risks, and benefits. Having a working knowledge of WLS procedures is important because it allows the evaluator to have a meaningful understanding of the challenges the patient has to face and allows an informed evaluation of patient's capacity to understand the expected health impact of WLS.

The American Society for Bariatric and Metabolic Surgery (ASMBS) has approved the following major WLS procedures: Laparoscopic Roux-en-Y Gastric Bypass (RYGB), biliopancreatic diversion with duodenal switch (BPD-DS), sleeve gastrectomy (SG), adjustable gastric banding (AGB), bariatric reoperative procedures (aka revisional surgeries), and open procedures as deemed appropriate by the surgeon [15]. These surgeries are categorized as restrictive (i.e., restrict the size of the gastric pouch leading to early satiety and thus lower caloric intake), malabsorptive (i.e., alter the gastrointestinal anatomy leading to reduction in absorption), or a combination of both (see Table 12.1).

In July of 2016, the ASMBS published an estimate of bariatric surgery volume and percentage of different procedures for the years 2011–2015 [16]. Figure 12.1 highlights the overall trends in WLS procedures performed. It illustrates the precipitous decline in the number of AGB procedures performed (from 35.4% to 5.7%) as bariatric programs have come to regard AGB as a less effective weight loss procedure due to the high rate of long-term complications leading to band removal, suboptimal weight loss, and high rate of obesity recurrence. The number of RYGB procedures has also significantly declined (from 36.7% to 23.1%) contributing to a significant increase in the number of SG procedures (from less than 20% in 2011 to more than half of all procedures performed in 2014). This trend toward laparoscopic SG continues as this procedure has proved its high efficacy and metabolic benefit with better side effect profile than the prior "gold standard" RYGB procedure. Some consider laparoscopic SG to be the new "gold standard" in WLS [17].

Interestingly, the number of revision surgeries has also more than doubled between 2011 and 2015 as AGB procedures have declined. Many revisions are for failed gastric banding procedures. The mental health provider evaluating a patient for revision surgery should have a clear understanding of the patient's original surgery, the reason for needing revision, and the prospective revision surgery offered.

Specific outcome measures reported after WLS include % total weight loss (%TWL), defined as operative weight minus the follow-up weight, divided by the operative weight and multiplied by 100; excess weight loss (EWL), defined as the operative weight minus the follow-up weight, divided by the excess weight and multiplied by 100; and excess weight (EW) defined as the operative weight minus ideal body weight based on a BMI of 25 kg/m^2. Inadequate WL is defined as %TWL < 20% at 12 months [18].

Presurgical Psychosocial Evaluation for WLS

Approximately 90% of bariatric surgery programs require their surgical candidate to undergo a preoperative psychosocial evaluation [19]. This is also a requirement by the majority of third party payers. While recommendations regarding the structure and content of the psychosocial evaluation have been published [20–22], there is no evidence-based standard of best practice for psychological evaluation of the patient undergoing WLS. Moreover, the predictive value of some of the domains assessed remains in question [23, 24].

Purpose of the Evaluation

The presurgical psychosocial evaluation for bariatric surgery is not solely intended to look for psychiatric disorders that may contraindicate the

Table 12.1 WLS procedures and their mechanism of action, advantages, and disadvantages

Procedure	Mechanism of action	Restrictive or malabsorptive[a]	Advantages	Disadvantages
RYGB	1. Creating a small stomach pouch 2. Bypassing the first portion of the small intestine	Both	1. Significant long-term weight loss (60–80% Excess Weight Loss (EWL) 2. Limits caloric intake 3. Metabolic changes that enhance energy expenditure 4. GI hormonal changes that enhance satiety 5. Typical maintenance of >50% EWL	1. More complex surgery 2. Higher complication rates 3. Longer hospital stay 4. Micronutrient deficiencies 5. Lifelong micronutrient replacement 6. Requires strict adherence
SG	1. Removing approximately 80% of the stomach 2. Creating a smaller stomach pouch 3. Altering GI hormones affecting satiety	Restrictive	1. Significant long-term weight loss, comparable to RYGB 2. Limits caloric intake 3. Metabolic changes that enhance energy expenditure 4. Relatively short hospital stay 5. No rerouting of the GI tract 6. Typical maintenance of >50% excess weight loss	1. More invasive than AGB 2. Micronutrient deficiencies 3. Not reversible 4. May worsen GERD
AGB	1. Creating a smaller stomach pouch by narrowing the inlet of the stomach with an adjustable band 2. Satiety depends on the size of the opening created (and adjusted) by the band	Restrictive	1. Limits caloric intake. (30–40% EWL) 2. No cutting or stapling of the gastrointestinal tract 3. The shortest hospital stay (less than 24 h) 4. Reversible 5. Least early postoperative morbidity and mortality 6. The lowest risk of micronutrient deficiencies	1. Lowest early weight loss 2. Slowest early weight loss 3. Foreign object remains in the body 4. Band slippage or erosion 5. Esophageal dilation 6. Requires strict adherence 7. Highest rate of revision surgeries 8. Highest rate of weight loss failure
BPD-DS	1. Creating a small stomach pouch similar to SG 2. Bypassing a large portion of the small intestine	Both	1. Greatest weight loss (60– 70% EWL a 5-year follow- up) 2. Reduces the absorption of fat by 70% or more 3. Gastrointestinal hormonal changes that enhance satiety 4. Most effective against diabetes	1. Higher complication rates 2. Higher risk for mortality 3. Longer hospital stay 4. Greatest risk of protein and micronutrient deficiency 6. Adherence to follow-up is critical

[a]As the metabolic effects of various WLS become better understood, this traditional classification has become less functional

proposed surgery [25]. By identifying psychosocial vulnerability of each WLS candidate, this evaluation develops a set of recommendations that enhance safe and effective WLS for each patient. A successful WLS provides the patient with the intended weight loss and improvement in both medical and psychological well-being. The evaluator should work with the patient to identify a patient's strengths and weaknesses and develop a plan that remediates those weaknesses and enhances strengths.

Occasionally, patients are resistant and uncomfortable with seeing a mental health provider as a prerequisite for WLS and therefore initially present as guarded or even antagonistic during the evaluation. Many patients begin the evaluation with a very limited understanding of the purpose of the evaluation and may be anxious

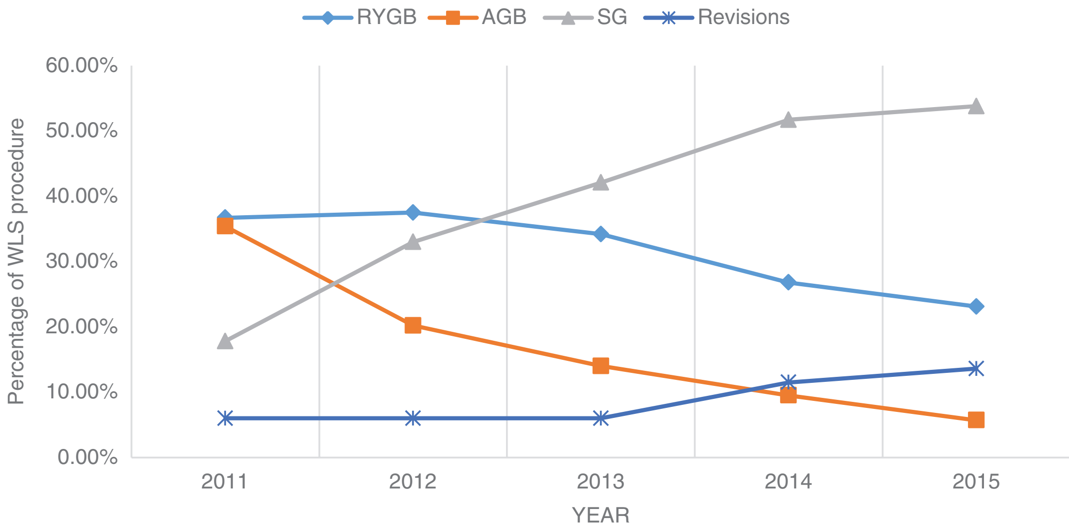

Fig. 12.1 Trends in WLS procedures

about the process [23]. On the other hand, a substantial proportional of WLS candidates present themselves in an overly favorable light during the psychological evaluation [26]. Both situations might interfere with the accurate assessment of symptoms and patient functioning. Thus, it is crucial to explain to the patient that the purpose of the interview is to facilitate their success post-surgically, not to potentially exclude them from WLS he or she desires, unless it is determined that there is a clear contraindication.

The Evaluating Clinician

Most WLS programs require candidates to undergo a preoperative psychosocial evaluation [19]. The terms psychosocial, psychological, and psychiatric evaluations are sometimes used interchangeably in the field. Also, there is significant variability in the credentials and experience of the clinicians performing those evaluations [27]. The psychosocial evaluation of WLS patients should be conducted by an individual who is professionally credentialed in a recognized behavioral health discipline (e.g., psychology, social work, psychiatry, psychiatric nursing, etc.). Furthermore, because this evaluation assesses several domains that are outside the regular psychological assessment, it is recommended that the evaluator also possesses specialized training, knowledge, and experience relevant to obesity, eating disorders, and WLS.

Timing of the Evaluation

When surgical candidates enroll in a WLS program, they must undergo preoperative evaluation for obesity-related comorbidities and causes of obesity, with special attention to those factors that could affect the outcome of the WLS. The preoperative evaluation includes a comprehensive medical history, physical examination, cardiopulmonary evaluation, gastrointestinal evaluation, endocrine evaluation, nutrition evaluation by registered dietitian, and psychosocial evaluation in addition to smoking cessation counseling if they use tobacco. In addition, they must continue efforts for preoperative weight loss [28]. There is no currently available literature on the appropriate timing of the presurgical psychosocial evaluation during the process. We recommend that the psychosocial evaluation be performed early in the process. In addition to screening out ineligible candidates, psychosocial evaluation provides the candidates with opportunities for education and motivation and allows the program to tailor a personalized plan for the patient. Based on the evaluation, if a patient requires psychosocial interventions that need time to be implemented, early identification will allow the patient to work on these recommendations with minimal delay to surgery date. Early evaluation may also have a positive impact on attrition rate of WLS candidates. On the occasion that a patient is deemed not to be a candidate for WLS, it is better for the patient and the program to establish this early in the process.

Additionally, the psychosocial evaluation should be done after the patient receives the necessary information about the procedure, including the expected postoperative life changes required. This is essential to evaluate a patient's ability to provide informed consent for WLS. When the patient has already been established in the program and has met with the WLS surgical team and the registered dietitian, it becomes much easier to establish the patient's understanding of the surgery's pre- and postoperative care, motivation, level of adherence, organizational ability, and many other aspects that will aid in making a decision and tailoring a personalized plan.

Domains of the Psychosocial Evaluation for WLS

The presurgical psychosocial evaluation for the WLS performed by mental health professionals varies widely. In general, a clinical interview, a thorough chart review, and collateral from family and providers are essential components of the presurgical psychosocial evaluation [20, 29]. A basic level of the clinical interview for WLS evaluates three major aspects: (1) understanding of WLS, (2) eating behaviors evaluation, and (3) psychosocial history (see Table 12.2). These domains will be discussed below.

Table 12.2 Major components of the presurgical evaluation for WLS

Understanding of the WLS
Motivations for seeking surgery
Knowledge of the surgery, its risks and benefits and the perioperative course
Expectations
Eating behaviors evaluation
Weight and diet history
Maladaptive eating behaviors not meeting diagnostic criteria for eating disorders
Psychosocial history
Psychiatric disorders
Adherence and organizational ability
Support system and social history

The Patient's Understanding of the Surgery

Motivations for seeking surgery

The evaluator should first clarify the patient's motivation to have WLS. Patients choose to undergo bariatric surgery for a variety of medical and psychosocial reasons. Patients seeking WLS need to have realistic expectations about the goals of surgery. Many patients report desire to lose weight to improve current medical problems, enhance mobility and energy, and promote health and longevity [30]. An overemphasis by the patient on body image and physical appearance warrants further exploration. It is also important to elicit any external pressure on the patient to have the surgery, e.g., from a parent, significant other, or physician. Further exploration is also warranted if the patient exhibits overoptimistic and otherwise unrealistic ideas regarding the expected outcome. Failure to address such expectations places the patient at risk of dissatisfaction, frustration, mood disorders, and nonadherence.

Knowledge of the Surgery: Risks, Benefits, and the Perioperative Course

The evaluator should assess the patient's understanding of the WLS being proposed. A significant number of WLS candidates present with misconceptions about WLS and weight loss in general. Patients should be informed about the surgical procedures available, the risks and benefits of each, and the postoperative behavioral program expected [28, 31]. While most patients will readily verbalize an understanding of the benefits of WLS, they commonly have a tendency to overlook or minimize the risks associated with WLS and the scope of the required behavioral changes. It is important to highlight to patients that the outcome of surgery is variable and heavily dependent upon consistent implementation of the recommended lifestyle changes [20]. Some patients have a cursory or inadequate understanding of the surgery and the nature of perioperative adherence required. The interview session should be utilized to provide education and formulate a plan to enhance the patient's knowledge. This plan may include providing reading material, scheduling additional meetings with the surgeon or the dietitian, or referral to the program's postoperative support group. This will ensure that the patient is adequately informed of the surgery, its risks and benefits, and postoperative behavioral requirements. While many patients seek the Internet to obtain information about WLS, it is important to inform the patients that some of the material offered online may not be medically accurate and can be potentially harmful.

Expectations

Most patients hold unrealistic expectations about how much weight they will lose after WLS [32–36], and weight loss expectations can be resistant to change [32, 37, 38]. One study found that women, Caucasians, younger patients, and those with higher initial BMI were more likely to have unrealistic goals [34]. Another study found that what patients considered to be a "disappointing" postsurgical weight—the most modest weight loss expectation identified by patients in the study—was equivalent to what providers would consider a successful weight loss outcome after WLS [35]. While data are mixed regarding the impact of weight loss expectations on weight loss outcomes, evaluating the patient's expectations and setting realistic expectations are important aspects of the preoperative evaluation and education [37, 39–44]. This is critical also for the purposes of informed consent [45], as informed consent should incorporate realistic projections of the short- and long-term risks, benefits, and consequences of surgery, as well as alternatives to WLS [31]. Unrealistic expectations may have negative influence on adherence and increase attrition rates postoperatively [33]. In a study by Homer et al., many patients felt that their expectations were not addressed adequately before surgery [46]. Specifically, the following issues should be discussed in exploring the patients' expectations:

1. The patient's goal weight
2. Anticipated time frame for achieving that goal
3. The potential for weight regain in the long term
4. The potential for developing excess skin
5. The degree to which weight loss will resolve pre-existing comorbidities
6. The degree to which weight loss will resolve psychosocial problems

Eating Behaviors

Weight and Diet History

During the psychosocial evaluation, the clinician should obtain a detailed history of the patient's weight trajectory over time [28, 47] to understand the medical, psychosocial, and environmental factors that contributed to obesity and that are likely to pose challenges for the patient postoperatively. This section of the evaluation also provides information about previous types of weight loss interventions that have been tried, duration of adherence to various approaches, and which factors may influence sustained behavioral change. [20, 48–50]. Guidelines published by the National Institutes of Health [51] and most third-party payers specify that WLS is an appropriate treatment option only when nonsurgical weight loss methods have failed; hence, the evaluator should document previous diets that the patient has tried in the past. Understanding the factors that have influenced the patient's previous dietary attempts helps formulate pertinent strategies for pre- and postsurgery weight loss.

The evaluator should gather information regarding the patient's eating habits such as food choices, portion size, tendency to rely on convenience foods, meal skipping, and frequent grazing vs interval snacks. It is also important to learn about the patient's organizational and self-care skills. Barriers to consuming healthy foods should be explored. The earlier a patient begins to implement healthier eating habits, the sooner logistical and other obstacles to such a lifestyle change may be identified in pursuit of weight loss goals. Successfully addressing such barriers early on improves the weight loss outcome as it provides the patient with a better cultivated path to weight loss.

The interviewer should also evaluate the patient's level of physical activity. This is often best explored with neutral, open-ended questions such as, "Tell me about your current physical activity patterns." This approach is less confrontational than, for example, "Do you exercise?". It also offers the clinician an understanding of the patient's physical activity level beyond planned and structured exercise.

This information helps the evaluator assess the ability of the patient to maintain a diet change or health-related behaviors that will enhance the chances for a good outcome post-surgery, such as medication adherence or regular exercise.

Maladaptive Eating Behaviors not Meeting Diagnostic Criteria for Eating Disorders

Exploring a patient's eating habits (preferences, dislikes, portion sizes, patterns, caloric content, triggers, etc.) is distinct from the formal assessment for eating disorders, yet is important because these habits may jeopardize desired weight loss by influencing postoperative adherence. Such eating habits may also shed light on a patient's ability to organize and maintain a structured eating pattern. Inquiring about changes that the patient has introduced in preparation for surgery can reveal a patient's understanding of and adherence to recommended behavioral changes. The patient's knowledge of the caloric content of different foods, ability to identify triggers for eating, hunger vs boredom is also a good indicator of the level of their informed consent especially when the patient has already started working with the dietitian. Grazing (the unstructured, repetitive eating of small amounts of food) is another behavior that needs to be screened for and addressed during the evaluations as this behavior in particular has been studied as a possible high-risk behavior that could predispose to binge eating postoperatively [52].

Psychiatric Disorder in WLS Patients

Psychiatric History

There is higher prevalence of psychiatric illness, particularly anxiety, depression, and binge eating disorder (BED), among candidates for WLS surgery compared to general population [53, 54]. Patients with severe obesity tend to exhibit more psychopathology than healthy weight individuals or those with less severe obesity [55]. The relationship between psychiatric diagnosis prior to WLS and postsurgical outcome (i.e., rate, amount, or sustainability of weight loss after surgery) remains unclear [23, 56]. Evidence suggests that there is a significant early decrease in the prevalence of psychiatric illness following WLS. Results from a study of obese Swedish subjects suggest that the most improvement occurs during the first year after surgery, followed by a decline in health- related quality of life (HRQL) from years 1 to 6, with eventual long-term stabilization. Improvements and deteriorations in HRQL were associated with the magnitude of weight loss or regain; however, anxiety did not exhibit association [57]. Two recent long-term studies suggest that this initial decrease in prevalence of psychiatric illnesses might reverse over time, despite both studies showing durable improvement in HRQL [58, 59]. One study found that initial improvement in neuroticism is more likely to revert [59]. The few studies that did not find a relationship between psychopathology before WLS and postsurgical outcome [60, 61] were relatively short duration (1–2 years) and did not include patients with severe psychopathology, as those patients would have not been cleared to have the surgery. Therefore, the severity of the psychiatric disorder rather than its mere presence plays a more influential role in determining surgery outcome.

The focus of the presurgical evaluation should be the impact that such symptoms or diagnoses have on presurgical preparation and postsurgical adherence and self-care [20]. The evaluator should inquire about diagnoses, their severity, current level of symptoms, duration of stability if relevant, the nature and severity of prior decompensations, as well as history of suicide attempts and prior psychiatric admissions. The evaluator should also inquire about the patient's current engagement in mental health treatment, if any, and level of adherence with the recommended treatment. The goal is not simply to identify diagnoses, but also to assess for the severity of symptoms and how these may hinder the patient's success. The evaluator should formulate a plan with the patient and, at times, the patient's mental health providers to optimize stability before surgery and ensure adequate monitoring for psychiatric symptom return or worsening postsurgery.

The literature consensus and practice guidelines consider current severe, untreated psychopathology to be a contraindication for WLS [20, 28, 62, 63]. One study demonstrated that a similar percentage of excess body weight loss can be achieved in patients undergoing LSG or LAGB despite the presence of well-controlled psychiatric comorbidity [64]. Delaying surgery in order to establish mental health treatment and improvement in psychiatric symptoms must be balanced with the health impact of extending the time lived with obesity and against the risk of patient not returning to WLS [65].

Adherence and Organizational Ability

Adherence to outpatient follow-up with surgical and medical appointments and adherence to aftercare recommendations following WLS have been associated with improved weight loss [66–68]. Moreover, inadequate adherence to follow-up care may lead to complications after bariatric surgery [69] with complete adherence resulting in a higher rate of comorbidity improvement and even remission rates compared with incomplete adherence [70]. One of the requirements for the Centers for Excellence program instituted by the ASMBS is to have a system in place to provide comprehensive follow-up care [71]. Attrition rates have been investigated in several studies and vary widely, depending on the type of operation and the nature and length of postoperative follow-up [72]. Despite the perceived importance of postsurgical follow-up and the high rates of follow-up attrition, little is known about the factors associated with long-term follow-up. In order to improve adherence and attendance rates, the factors leading to poor adherence and those improving adherence need to be identified. Developing a clearer understanding of such predictors and incorporating them into preoperative screening tools would ideally help identify patients at risk of nonadherence and ultimately improve follow-up care. Some risk factors of attrition that have been considered include age, gender, distance traveled, BMI, mental health, and various psychological symptoms. Ultimately, though, the eight studies to date have yielded inconsistent findings on risk factors for attrition [72]. As is common across studies on the psychological and behavioral aspects of WLS, the studies in this area have enrolled heterogeneous cohorts undergoing different types of bariatric surgery, employed different study methodology, and assessed different outcome variables. Often, past adherence patterns should provide a good indicator on the patient's postoperative adherence [20]. Patients should be educated about the critical value of adherence to postoperative care, and any potential barriers to future adherence should be explored with the patient in an attempt to improve postoperative adherence and favorable outcome.

Support System and Social History

Robust social support has been found to result in better patient self-efficacy, which, in turn, contributes to better medical adherence and better outcomes in various medical conditions [73–75]. Social influences play a crucial role in patient's dietary behavior. [75]. For instance, having a reliable social network can support healthy behavior by providing models to emulate, addressing the patient's concerns, enhancing self-esteem, relieving them of daily responsibilities, and offering them companionship in their bariatric journey [76]. Perceived support from family and friends was found in one study to be associated with greater weight loss after bariatric surgery [77]. Another study of adolescents undergoing sleeve gastrectomy found that more social support was associated with more exercise and less binge eating [78]. The impact of WLS upon family relationships needs to be further investigated. The common belief is that WLS will improve one's marriage.

Whereas some studies have found success after bariatric surgery to be associated with a satisfactory marriage [79, 80], one study suggested that the quality of couples' relationship tended to decline after WLS, while sexual contact increased post-WLS [81]. Thus, the clinician should explore the patient's support systems including romantic relationships, partners, and spousal relationships and provide education and counseling on this important issue. Woodard et al. looked at the rate of obesity in families of patients having RYGB. They found that before RYGB, 60% of adult family members and 73% of children of patients undergoing Roux-en-Y gastric bypass surgery were obese. Interestingly, the study found that at 12 months after WLS, significant weight loss was observed in obese family members, both adults and children. In addition, family members increased their daily activity levels. Also, adult family members had improved eating habits, a phenomenon described "as the halo effect" [82].

Special Considerations

During the interview, the clinician should keep in mind that the evaluation is a snapshot of the patient. Thus, the clinician should seek any information regarding the patient's past medical, psychiatric, and social history available in the patient's medical record in addition to obtaining collateral from outpatient providers and family members. Relevant information includes previous diagnoses, adherence to treatment (including keeping appointments), communication style, weight flowsheets, glycemic control, and medications. This information will offer the clinician context and relevant background. Fortunately, obtaining such information has become easier to with the prevalent availability of electronic medical records.

Common Psychiatric Disorders Among WLS Candidates

Eating Disorders

The patient's weight history is closely related to the history of eating behavior. Preoperative eating pathology and eating disorder diagnoses impact outcomes after WLS; however, variations in study design, population, and outcomes of interest across studies make it difficult to draw definitive conclusions [20]. Recent changes in the diagnostic criteria for some of these disorders from DSM-IV-TR to DSM-5 also make it difficult to apply study findings to a given patient. Although published practice guidelines and expert opinion broadly recommend assessment of past and current eating disorder symptoms [20, 22, 65, 83], it should be kept in mind that the presence of such symptoms does not represent an absolute contraindication for WLS. [20, 28, 49, 84]. This chapter will present the most common eating disorders including their diagnostic criteria, known prevalence, treatments available, and their impact upon WLS outcomes when known.

Binge eating disorder (BED) is defined by the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) [85]. Its diagnostic criteria include:

(A) Recurrent episodes of binge eating (eating in a discrete period of time a portion that is larger than what most people would eat in a similar period, with sense of loss of control over eating)
(B) Associated with three of the following: eating rapidly, until feeling uncomfortable, eating large portion when not feeling hungry, eating alone because of embarrassment, feeling disgusted with oneself, depressed, or guilty afterward
(C) Marked distress over binge eating
(D) Binge eating episodes occurring at least once a week for 3 months
(E) Binge eating in the absence of compensatory behaviors

BED is the second most common psychiatric disorder in bariatric surgery populations, following major depressive disorder, [86] and it is the most commonly researched eating disorder associated with WLS. It is the most common eating disorder in candidates for WLS with approximately 25% meeting the DSM-IV-TR criteria [87]. Estimates of the prevalence of BED and subthreshold BED diagnosis in WLS-seeking samples vary widely, ranging from 2% to as high as 49% [20, 87–90]. The wide range of prevalence results from high variability in the study design and the fact that the diagnostic criteria changed as the field transitioned from DSM-IV-TR to DSM-5.

Emerging literature highlights that the clinical significance of binge eating is related more to the experience of loss of control while eating rather than portion size [20, 84, 91–93]. Inconsistent findings suggest a potential relationship between preoperative BED and postoperative weight loss [23, 24, 94–97]. Interestingly, the studies that did not identify an association between preoperative BED and post-WLS outcome were shorter in duration and emphasized total weight loss to the exclusion of other relevant outcomes such as eating pathology, depression, or overall quality of life [98–100].

It is important to explore the factors that trigger BED episodes, whether binges are triggered by uncontrolled hunger which arises from irregular, chaotic eating patterns or if they are emotionally triggered [101]. Emotional eating negatively affects postoperative weight loss and is more resistant to treatment [102]. Postsurgery, it is important to differentiate eating behaviors that occur as side effects of the procedure from more pathological eating-related behavior [83]. Some common behaviors seen after WLS can be interpreted as symptoms of an eating disorder. For example, frequent vomiting in response to "plugging," which is a subjective sensation that food is stuck in the patient's pouch, can be confused for an eating pathology. Dumping syndrome is another common side effect following WLS. Dumping syndrome can occur when patients consume foods with high sugar or carbohydrate content and is characterized by nausea, vomiting, and diarrhea in addition to vasomotor symptoms [103]. Vomiting and dumping syndrome decrease as patients adapt to postsurgical changes. However, these behaviors should be monitored, as some patients will self-induce them as a means to continue weight loss or prevent weight gain [104–106]. Management of patients with BED or subthreshold BED diagnosis comprises educating patients about the risks of eating pathology reemerging after surgery, providing long-term postsurgical monitoring and providing treatment resources [20]. All BED patients should receive appropriate management prior to proceeding with WLS. This includes pharmacotherapy [107, 108], mindfulness, cognitive behavioral therapy, and dialectical behavioral therapy. Mild to moderate BED should not be viewed as a contraindication for the surgery and management should not delay the surgery. Leahey et al. found that patients who were referred for the treatment after undergoing surgery were significantly more likely to complete the treatment and attended significantly more treatment sessions than did their counterparts who received referrals for the treatment prior to undergoing surgery [109].

Bulimia nervosa (BN) is defined by DSM-5 [85] by the following criteria: (A) recurrent episodes of binge eating; (B) recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise; (C) the behavior that occurs at least once a week for 3 months; and (D) self-evaluation is unduly influenced by body shape and weight. Presurgical BN is rare among WLS candidates and, untreated, is often considered a contraindication to these surgical procedures [20, 21, 28]. Chen et al. found the presence of presurgery compensatory behavior to be a small but significant predictor of lower BMI 6 months postsurgery but not at 1-year postsurgery [110]. After WLS, the modified anatomy of the upper GI tract might even promote the development of new eating pathology after surgery. Patients might experience involuntary vomiting during the first few postoperative weeks. During that period, they frequently discover that they can vomit with ease after eating, and a significant minority of patients develop de novo eating pathology (anorexia nervosa, BN, or subsyndromal eating disorder) [104, 106]. Clinicians must actively screen for these behaviors postoperatively in order to identify patients in need of treatment of pathological eating behaviors.

Night eating syndrome (NES) is an eating disorder characterized by a delayed circadian pattern of food intake. The specific criteria for NES has not been universally agreed upon, but there has been proposed criteria. In DSM-5, it is included under "Other Specified Feeding or Eating Disorder" [85]. These criteria are:

1. Recurrent episodes of night eating, as manifested by eating after awakening from sleep or by excessive consumption after the evening meal.
2. There is awareness and recall of the eating.
3. The night eating is not better explained by external influences such as changes in individuals' sleep-wake cycle or by local social norms.
4. The night eating causes significant distress and/or impairment in functioning.
5. The disordered pattern of eating is not better explained by binge eating disorder or another mental disorder, including substance use, and is not attributable to another medical disorder or to an effect of medication.

Allison et al. proposed similar criteria based on an international night eating symposium held in Minneapolis, Minnesota, in 2008 [111].

The core feature of NES is the delayed circadian shift of eating [112]. The prevalence of NES pre-WLS varies significantly between studies, ranging from 1.9% [88] to 17.7% [113]. The reported ranges are broad in large part due to the use of inconsistent diagnostic criteria across studies. Without a consensus on diagnostic criteria, NES has been defined with varying cut-off times, percentages of evening hyperphagia, and required frequency (if at all) of night eating episodes [114, 115]. Some studies have found that NES rates are maintained after surgery [116], while other studies found that NES rates decrease postoperatively [117, 118]. Interestingly, in one study, six out of ten patients developed de novo NES postoperatively [117]. No data yet support NES as a risk factor for attenuated weight loss after WLS [118–120]; thus, its presence preoperatively is not considered a contraindication for proceeding with WLS. Even still, the presence of NES postsurgery has been associated with higher BMI and lower satisfaction with results [118]. Although the role of NES remains incompletely understood in relation to WLS and postsurgical outcomes, NES deserves proactive assessment, intervention, and ongoing postsurgical monitoring, at the very least for its known comorbidity with psychiatric symptoms [20].

Many treatments have been considered for NES. For instance, an open-labeled nonblinded 12-week trial found that sertraline reduced nighttime awakenings, night snacking, and evening energy consumption in 17 obese NES subjects [121]. A reduction in night eating has also been reported following administration of d-fenfluramine [122]. A relaxation intervention (abbreviated progressive muscle relaxation therapy, APRT) has been reported to significantly reduce stress NES [123]. Finally, NES should not be confused with sleep-related eating disorder (SRED), which is a type of non-REM-related parasomnia [124]. Patients with SRED are sleepwalkers who happen to eat, whereas patients with NES are those with binge eating disorder who happen to eat at night while awake [125]. These two distinct conditions frequently co-occur [96], and polysomnographic findings can overlap [126].

Anxiety, Mood and Psychotic Disorders

Anxiety Disorders are common psychiatric diagnoses among patients seeking WLS [127, 128]. While studies indicate that psychiatric symptoms may improve postoperatively [129], anxiety symptoms seem to be the most resistant to improvement [130] and more likely to reemerge 10 years later [59]. In addition, untreated anxiety, such as agoraphobia or social phobia, can negatively affect postoperative participation in care [131, 132].

Posttraumatic stress disorder (PTSD) has been associated with obesity [133, 134], but the reasons for this association remain unclear. Proposed mechanisms in which childhood trauma leads to obesity later in life can be categorized as biological (e.g., inflammation, the renin-angiotensin-aldosterone system, and neuroendocrine activation) or psychological pathways (such as psychopathology, lifestyle decisions, substance use, other behaviors) [135] . Conversely, there are no studies to date examining if obese individuals are predisposed to developing PTSD compared to the general population [133], but the relationship between bullying and obesity has been well-documented [134], and the suggestion has been made that obesity may lead to being a victim of bullying and trauma [136]. A history of PTSD and child sexual abuse has been found to have little influence on postoperative weight loss [137–139], but history of sexual abuse was found in one study to increase the number of psychiatric hospitalizations after bariatric surgery [138]. PTSD is not a contraindication for WLS, but it warrants special attention, patient education, and not uncommonly referral to psychiatric care.

Depressive Disorders: Despite an abundance of studies investigating depression in WLS candidates [140], the mechanisms that account for the comorbidity of obesity and depression remain incompletely understood. Few studies have found depressive symptoms to be negatively associated with weight loss postsurgery [141, 142]. These studies enrolled small cohorts and typically did not follow patients beyond 1 year after surgery. Many studies, on the other hand, did not find significant association between depression and its severity and the percentage of EWL [143–145]. Interestingly, two studies have found dysthymia and a high score on the Beck Depression Inventory to be associated with greater weight loss following WLS [146, 147].

The development of depression postsurgery is a stronger predictor of postsurgical outcome than preoperative diagnosis of depression [148]. Relative to anxiety symptoms, depression is more common to remit during the first 2 years after surgery, which coincides with the peak weight loss. Unfortunately, at 10-year follow-up, depression may reemerge [57, 130, 149]. As with any psychiatric evaluation, a history of suicidal ideation, prior suicide attempts, and history of self- harm should be assessed.

Increased rates of suicide and self-harm risk in post-WLS patients have attracted attention in recent years. One Canadian study found that the risk of self-harm emergencies including intentional overdoses significantly increased after bariatric surgery (relative risk [RR] 1.54) [150]. A separate study in the USA, looking at completed suicides, found that there was a substantial excess of suicides among all patients who had bariatric surgery compared with age- and sex-matched suicide rates in the USA during a 10-year period. The overall rate of completed suicides was 6.6/10,000; 13.7/10,000 among men and 5.2/10,000 among women. About 30% of suicides occurred within the first 2 years following surgery, with nearly 70% occurring within 3 years. For every age category except the youngest, suicide rates were higher among men than women [151]. While history of suicide attempt warrants very close attention including monitoring of mood symptoms and ongoing screening for suicidal ideation postoperatively, current evidence does not support regarding a historical suicide attempt as an absolute contraindication to WLS, nor is it clear in the literature how long a patient should be free of suicidal ideation or attempts before proceeding to surgery [20].

Schizophrenia and bipolar disorder patients are at a 2–3 times increased risk of developing metabolic disorders including obesity, diabetes, and hyperlipidemia, which accounts for the largest portion of their 10–20-year reduction in life expectancy [152, 153]. The increased metabolic and cardiac risk in this cohort appears to be due to a combination of genetic factors, oxidative stress, socioeconomic privation, lifestyle choices, eating disorders, and potential metabolic effects of many psychotropics [154, 155]. Whereas WLS has been proven to be the most effective durable weight loss method, it has not been routinely offered to patients with severe mental illness including bipolar disorder or schizophrenia [49, 140, 156]. This may reflect providers' implicit bias, a concern that these patients are unable to adhere to recommended lifestyle changes, despite limited evidence to substantiate this assumption [157]. In addition, the risk of malabsorption of pharmacological treatment after surgery is a relevant concern, one that very few studies have addressed in postsurgical cohorts [158]. One study found that patients diagnosed with a bipolar-spectrum disorder have a high rates of delay and denial for bariatric surgery based on psychosocial evaluation (57% were approved and 48% ultimately had surgery). Denied patients were more likely to have had past history of psychiatric hospitalization. Bipolar patients were also found in this study to be less likely to attend medical follow-up care 2 or more years postsurgery. Even still, among patients who were available for follow-up evaluation, bipolar-spectrum disorder was associated with comparable weight loss at 12 months and at 2 or more years compared with matched controls [159].

A recent large, 2-year study found that WLS did not adversely impact the psychiatric course or treatment of patients with bipolar disorder [160]. Similarly, one study following five patients with a diagnosis of schizophrenia found that the results of bariatric surgery in such patients are comparable to those of morbidly obese patients without a psychotic illness [161]. A recent literature review looking at WLS among patients with schizophrenia and bipolar disorder found that weight loss from bariatric surgery was similar in people with schizophrenia or bipolar disorder versus controls. However, most of the studies limited their outcomes only to weight loss and did not measure whether WLS affected the status and treatment of psychiatric symptoms [157].

Substance Use Disorders

Substance use disorders (SUD) should be assessed during psychosocial evaluation [20, 83].

WLS candidates have a greater *lifetime* history of SUD than the general population (32.6% vs 14.6%). However, *active* alcohol and other SUD are remarkably low (<1%) compared with population prevalence (8.9%) [162]. While the low rates of active SUD in WLS candidates could represent true remission, patients may also be underreporting active substance use due to concerns about delays in surgery due to active substance use. An active SUD is generally considered a contraindication to WLS [63, 163], whereas lifetime history is not, provided an adequate period of abstinence has been maintained [164]. Two studies suggest that presurgical history of successful abstinence was associated with greater postsurgical weight loss [165, 166]. One might speculate that these patients, having already made and benefitted from comprehensive, sustained behavioral change, were able to make similar changes pertinent to weight loss. Zhou et al. identified several risk factors of developing a new SUD after RYGB surgery. These include male sex, younger age, low interpersonal support, presurgical food addiction, intake of high glycemic index and high sugar/low fat food, family history of a SUD, presurgery tobacco use, postsurgery recreational drug use, regular alcohol consumption before surgery, and history of alcohol use disorder in the 12 months prior to surgery [167].

Alcohol use disorder (*AUD*) has emerged as a significant risk for individuals who have undergone WLS, and it is the most studied SUD in the WLS patient population. King et al. found an 11.3% prevalence of AUD per DSM-IV-TR among patients following RYGB, and it has been associated with twice the risk of incident AUD symptoms relative to AGB [168]. One study found the prevalence of AUD to be greater in the second postoperative year than the year prior to surgery or in the first postoperative year; in this study, risk factors for AUD included male sex and younger age [168]. Other studies have also found an increased risk after the second year postoperatively compared to the first year [169, 170]. This warrants the utilization of screening tools for AUD in post-WLS patients, since about two thirds of cases of post-WLS AUD occur de novo in patients who have had no history of such problems before surgery [169, 171]. The use of screening tools for AUD (e.g., CAGE or AUDIT) during routine medical follow-up visits should be considered. Patients with current heavy alcohol consumption within 1 year before the surgery and those with active AUD at the time of WLS are at higher risk for continuation of AUD post-WLS. The ASMBS recently issued its position statement on alcohol use before and after bariatric surgery, and a summary of its recommendations is as follows [164].

1. There is conflicting data as to the lifetime and current prevalence of AUD in patients seeking WLS (see Table 12.3).
2. Gastric bypass surgery is associated with:
   (a) Accelerated alcohol absorption (shorter time to reach maximum concentration)
   (b) Higher maximum alcohol concentration
   (c) Longer time to eliminate alcohol in both men and women
   (d) Increased risk for development of AUD
3. The data are less clear regarding altered pharmacokinetics after sleeve gastrectomy, and there is no evidence that alcohol absorption is affected by gastric banding.
4. Patients undergoing bariatric surgery should be screened and educated regarding alcohol intake both before and after surgery. Active AUD is considered a contraindication by most programs and in published guidelines. Adequate screening, assessment, and preoperative preparation may help decrease the risk of AUD in bariatric surgery patients. A period of sustained abstinence with treatment is indicated before WLS. A history of AUD is not a contraindication to bariatric surgery. However, patients should be made aware that AUD can begin or reoccur in the long term after bariatric surgery.

Table 12.3 Studies on the prevalence of alcohol use and AUD before and after WLS [164]

Summary of the literature of AUD/high-risk drinking before and after bariatric surgery				
Author	Year	AUD/high-risk drinking	*n*	Results
Ertelt et al.	2008	7.1% preoperative; 2.9% postoperative (new onset)	70	Questionnaires, 28% response
Saules et al.	2010	2–6% of admissions to substance abuse facility positive for bariatric surgery history	54 (matched)	Relative to matched controls, the alcohol-dependent bariatric surgery patients consumed more drinks
King et al.	2012	7.6% preoperative; 7.3% postoperative (1 year); 9.6% postoperative (2 years)	1945	Prospective cohort study (LABS); AUD associated with male, young age, smoking, preoperative AUD, drug use, and undergoing RYGB
Suzuki et al.	2012	35.3 lifetime, 11.8% current	51	Higher current AUD in patients with lifetime AUD and in patients undergoing RYGB
Conason et al.	2013	2.3% baseline; 3.2% postoperative (2 years)	155	Higher frequency of alcohol use in RYGB patients; however, low response rate at 2 years (24%)
Wee et al.	2014	1 year: 13% reported high-risk drinking versus 17% baseline ($P = 0.10$) 2 years: 13% reported high-risk drinking versus 15% baseline ($P = 0.39$)	375 (1 year); 328 (2 years)	At 1 and 2 years, 6% and 7% reported new high-risk drinking. At both time points, more than half of those who reported high-risk drinking at baseline no longer did so
Svensson et al.	2013	93% of surgery patients had alcohol consumption classified as "low-risk"	2010 (matched)	Compared with controls, RYGB patients had an increased risk of alcohol abuse/consumption.
Ostlund et al.	2013	4.4–4.7% incidence of inpatient treatment of alcohol abuse preoperative	11,115	Postoperatively: patients undergoing gastric bypass had more than double the risk (HR 2.3, 95% CI 1.7–3.2) of inpatient care for alcohol abuse compared with restrictive procedures

Abbreviations: *AUD* alcohol use disorder, *CI* confidence interval, *HR* hazard ratio, *LABS* longitudinal assessment of bariatric surgery, *RYGB* Roux-en-Y gastric bypass

Other substance use disorders should be also carefully evaluated as presurgery lifetime SUD rates from the Longitudinal Assessment of Bariatric Surgery-2 (LABS-2) for cannabis, stimulants, cocaine, and polysubstances which were 7.5%, 3.5%, 2%, and 1%, respectively [172]. Cannabis use and its association with increased appetite and BMI are well-studied, but whether cannabis use influences outcomes in the bariatric population remains largely uninvestigated. In one study, marijuana use was found not to have a measurable effect on 90 days outcomes[1] after bariatric procedures, although the brevity of study follow-up limits the scope of conclusions. This study also found that cannabis users received higher doses of perioperative opioids than controls [173]. The legalization of "medical marijuana" in many states has posed a new challenge for the evaluator, as its effect on body weight remains unknown [174].

Another challenge for the clinical evaluation WLS candidates is posed by methadone-maintained patients with opioid use disorder in full sustained remission. Patients entering methadone maintenance therapy often gain significant weight. For instance, one study found that women 2 years into treatment had an average weight increase of 17.5% [175]. Despite this, due to a variety of concerns such as higher risk of dropout before WLS [176], fear of adverse outcomes, uncertainties concerning the effects of the procedure on pharmacokinetics, or fear that these patients will require significantly higher doses of opioid analgesics, many surgeons and WLS programs are reluctant to offer WLS to patients on methadone maintenance. Thus, morbidly obese patients on methadone maintenance are at risk for WLS refusal, or they may be required to discontinue methadone, placing them at risk of opioid relapse or other complications [177]. There are few studies investigating opioid use (and, by extension, methadone maintenance) and WLS. A recent study looking at opioid use after bariatric surgery found that the prevalence of prescribed opioid analgesic use initially decreased, but then increased to surpass baseline prevalence (prevalence of opioid use decreased after surgery from 14.7% at baseline to 12.9% at month 6 but then increased to 20.3%, above baseline levels, as time progressed at year 7 post-WLS) [178]. One case report of a patient on methadone maintenance undergoing SG found that methadone concentrations had increased from preoperative levels on postoperative day 5. In fact, methadone levels continued to increase for 7 months thereafter, suggesting that serum concentration be measured serially to prevent supratherapeutic levels [179]. In the absence of consensus guidelines on the use of medical marijuana or methadone in this population, patients should be evaluated on a case-by-case basis, taking into consideration the indication for use of either medical marijuana or methadone maintenance, abstinence from other drugs, and the effect of prescribed methadone or marijuana on the patients' cognitive and organizational ability.

Tobacco use disorder is a DSM-5 diagnosis assigned to individuals who are dependent on the drug nicotine due to the use of tobacco products. Among WLS candidates, prevalence rates of tobacco use are estimated to be as high as 38%, and of these, 57% are heavy smokers (i.e., >25 cigarettes a day) [180]. The ASMBS and the American Association of Clinical Endocrinologists (AACE) recommend smoking cessation before WLS [20, 28], which is the standard policy in most WLS programs. While the optimal period of smoking cessation pre-WLS remains undefined [181], AACE/The Obesity Society (TOS)/ASMB recommend at least 6 weeks of smoking cessation. Several studies suggest that rates of cigarette smoking in WLS patients do not significantly change pre- and post-bariatric surgery [182–184]. Young adults undergoing WLS are less likely to quit cigarette smoking after surgery compared to older patients [183]. Cigarette smoking is associated with increased risk of poor wound healing, anastomotic ulceration, and overall impaired health. Interestingly, two small studies found that 9.6–12.1% of patients may experience de novo cigarette smoking after WLS [180, 184]. The evaluator should provide education regarding

[1]The primary outcome was weight loss at 90 days, and other clinical outcomes included ED visits and readmissions, post-WLS, and the use of narcotic pain medications.

short- and long-term risks of smoking and offer resources for smoking cessation. Younger individuals, especially those with history of smoking, should be periodically screened for smoking postoperatively. It also seems that complications related to smoking are more pronounced following RYGB surgery compared to smoking-related postoperative complications with sleeve gastrectomy [185, 186]; thus, sleeve gastrectomy may be preferred if the patient is at high risk of relapse on tobacco.

Personality Disorders

Personality disorders have been studied as potential risk factors for obesity. A systematic review of literature on predictors of weight loss following WLS found that personality disorder diagnosis might be negatively associated with weight loss (7 out of 14 studies reviewed) [142]. Unfortunately, most of the studies on the association between personality disorders and WLS did not specify which personality disorders or whether a specific personality disorder has more correlation than the others. Prevalence of personality disorder diagnosis among WLS candidates ranges from 19.5% to 28.5% with cluster C personality disorders being most common [162, 187, 188]. Cluster A is described as the odd, eccentric cluster. It includes paranoid, schizoid, and schizotypal personality disorders. The common features of the personality disorders in this cluster are social awkwardness and social withdrawal. Cluster B (borderline, antisocial, histrionic, and narcissistic personality disorders) is characterized by dramatic and overly emotional or unpredictable behavior. These patients tend to react poorly during times of stress, especially when the postsurgical recovery is difficult, and require more frequent follow-up after the surgery for psychological support. Prior to the WLS, providing clear written instructions which delineate expectations for both the patient and the treatment team is helpful. Cluster C personality disorders, often referred to as the anxious and fearful personality disorders cluster, include the avoidant, dependent, and obsessive-compulsive personality disorders. Studies on the impact of personality disorders on WLS outcomes remain inconclusive [20]. At present, a diagnosis of personality disorder is not a contraindication to proceed with bariatric surgery, but given this cohort's enduring and pervasive interpersonal difficulties and poor general level of functioning, with some clusters exhibiting propensity for mood lability, impulsivity, and self-injurious behavior, they warrant special attention.

Neurodevelopmental and other cognitive disorders. Literature has reported strong association between obesity and attention-deficit/hyperactivity disorder (ADHD) both in adolescents [189] and adults [190, 191]. In a German study of obese individuals in the general population, 9.7% screened positive for ADHD [190], and prevalence of ADHD in pre-bariatric surgery patients has ranged from 7% to 12.1% [192–195]. Cognitive difficulty, particularly with executive functioning, may impede one's ability to maintain a healthy weight due to difficulty with planning, organization, and impulse control. In addition, symptoms of adult ADHD have been associated with elevated alcohol consumption after surgery [194].

Reports of successful WLS for patients with mild to moderate intellectual disability (ID) exist. A recent report in Brazil describes two successful cases of WLS in patients with ID. One with Prader-Willi syndrome (IQ 54) who had biliopancreatic diversion (BPD) and another with Down syndrome (IQ 68) who had RYGB. Both patients had significant weight loss 2 years postoperatively with resolution of comorbidity in one of the cases [196]. Gibbons et al. reviewed the literature on WLS procedures performed on individuals with ID. Reviewers included 16 studies, both case reports and case series. Among these reports, the most common procedure was BPD followed by RYGB. The degree of weight loss was the primary outcome in each study. EWL ranged from 12% to 86% with other benefits including improved quality of life, decreased psychological tension within family, and resolution of multiple comorbidities [196]. Severe ID (IQ < 50) was found by a survey in 2005 to be one of the most commonly cited contraindications for WLS due to concerns of inadequate knowledge about WLS and unrealistic expectations for weight loss [19].

There were no studies to date looking at WLS for patients with mild cognitive impairment, dementia, or brain injury. On the other hand, many studies found that cognitive function may improve up to 3 years after bariatric surgery [197, 198]. In fact, one recent study suggests that WLS may reduce the risk of Alzheimer's diseases through GLP-1-mediated neuroprotective effects [199].With WLS becoming more widely available and more commonly offered to patients with neurointellectual disability or cognitive impairment, evaluators are increasingly being called upon to perform preoperative assessment on patients with these comorbidities. Assessment of this population requires careful attention to the patient's understanding of the procedure, their ability to adhere to pre- and post-WLS care, and other patient-specific factors.

Psychopharmacology and WLS

WLS patients have a high level of psychiatric comorbidity, with the prevalence of any primary psychiatric disorder approaching 40% [162]. In studying changes in prescription drug use after bariatric surgery, Gribsholt et al. found large reductions in the use of medications for metabolic syndrome-related conditions as well as for inhalers and glucocorticoids for obstructive airway diseases 3 years after RYGB surgery. In contrast, the use of neuropsychiatric medications *increased* after RYGB [200]. Antidepressants are the most frequently prescribed type of psychotropic medication in this population and are commonly continued after surgery [201, 202]. As bariatric surgery becomes more widespread and accessible, the number of patients on psychotropic medications who undergo bariatric surgery will increase. This means that clinicians working in WLS programs should be familiar with a variety of psychopharmacological management issues in this population.

As discussed earlier, WLS procedures are predominantly restrictive, predominantly malabsorptive, or a combination of both (see Table 12.1). Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) are the two most commonly performed WLS procedures in the USA. Despite the emerging popularity of SG, the literature regarding psychopharmacology after WLS has focused on RYGB. Although this is largely due to RYGB's historical predominance, it is also notable that RYGB has mixed restrictive and malabsorptive effects, each of which uniquely alter the pharmacokinetics of enteral medications due to changes in GI structure and function.

Pharmacokinetics is the effect of the body on an externally administered substance. It encompasses (1) absorption of the substance into the blood circulation, (2) distribution of the substance throughout the body fluids and tissues, (3) the body's metabolism of the substance into a more readily excretable products, and (4) excretion whereby the substance is removed from the body. Here we review the effect of bariatric surgery on each of these steps.

Absorption

Of the pharmacokinetic changes of post-WLS, absorption is often altered the most [203]. Padwal et al. describe the steps involved in drug absorption and the theoretical impact that bariatric surgery has on these [204]. For a drug to be absorbed into systemic circulation, it goes through the different steps (see Table 12.4).

In one of the only formal studies of its kind, Seaman et al. conducted an in vitro drug dissolution trial that involved psychotropic medications [206]; of the 22 psychotropic drugs evaluated, 12 dissolved differently in the post RYGB versus control conditions. Given the many variables affecting the absorption of medications, parenteral agents continue to be a reliable method of medication administration where enteral absorption is compromised. Also, it is judicious to obtain individual drug level when feasible.

Table 12.4 Steps of drug absorption and the impact of bariatric surgery

Process	Definition	Impact of bariatric surgery
Disintegration	Dissolution in the stomach	↑ gastric pH and ↓ gastric mixing
Gastric emptying	Emptying from gastric pouch to the small intestine	↓ pouch size and gastric stoma
Absorption	Exposure to the intestinal mucosa and transport across the epithelium by either passive diffusion or active transport	Most drug absorption occurs in the small intestine where duration of drug/mucosal contact is the most important factor [205]
Emulsification	Bile acid mixing with lipophilic drugs to increase solubility	Decreased in RYGB
Metabolism	The body's manipulation of the drug into a more readily excretable products	Malabsorptive procedures involving different portions of the intestine may produce variable changes in drug absorption [205]

Distribution

Distribution is the process by which a medication enters the body's interstitial and intracellular fluids. Drug distribution after WLS can be influenced by vascular volume, cardiac output, plasma protein binding, tissue volume, and tissue binding [205]. Also, a drug's volume of distribution will change depending on its affinity for adipose in addition to the patient's change in lean body mass (LBM). The two major ways in which volume of distribution may change following WLS are through changes in body weight and composition following surgery and through changes in drug binding vis-à-vis plasma protein concentration. A drug bound to plasma proteins is retained in plasma, unable to penetrate through membranes, and therefore unable to enter tissues and reach the sites of action and produce a pharmacological effect [207]. Because the free (unbound) drug accounts for pharmacological activity, a decrease in plasma protein concentration can increase the free fraction of the drug. This is most pronounced with highly protein-bound medications.

The two plasma proteins that account for the most binding are albumin and the acute phase protein alpha-1-acid glycoprotein (AAG). WLS does not typically cause significant protein-calorie malnutrition and associated hypoalbuminemia [208, 209], but it still may occur [210]. AAG, on the other hand, is known to decrease in response to rapid weight loss, as in WLS, and has been shown to change significantly 12 months postsurgery [211, 212]. AAG, and to a much lesser extent, albumin, may be reduced in patients post-RYGB thus leading to increased unbound drug concentration. These changes can affect medications' effectiveness and increase their adverse effects, leading to toxicity.

Metabolism

Metabolism involves drug alterations that facilitate excretion and ultimate elimination from the body. Drug metabolism occurs primarily in the liver by oxidation, reduction, and hydrolysis (phase I) and/or conjugation (phase II) [213].

Excretion

A drug is then eliminated through the urine, bile, feces, and or other bodily fluids. Obesity is associated with nonalcoholic fatty liver disease, which is present in the majority of pre-WLS candidates. In fact, 25% of WLS candidates have nonalcoholic steatohepatitis (NASH), a necro-inflammatory and fibrotic condition. WLS—especially RYGB—improves NASH, but early in the rapid weight loss phase, worsening of inflammation may occur [214]. Rapid weight loss may also be associated with changes in renal drug clearance [205], a factor that could affect the blood levels of renally excreted medications.

Medication Formulations

Psychotropic medications may be administered in enteral and parenteral formulations. Enteral formulations can be immediate-release, extended- or delayed-release, orodispersible (also known as orally disintegrating), and liquid formulations. Selection of enteral formulation is especially important in this patient population due to changes in GI function and anatomy. Extended-release formulations are intended to minimize the number of individual doses and minimize side effects, thus improving effectiveness and adherence. However, following WLS, delayed-release formulations may not be well absorbed as they may not remain in the shortened GI tract for a sufficient amount of time to permit adequate absorption [204, 215]. Moreover, in the acute postoperative setting, often all medications must be crushed, causing many medications to lose their extended-release property. Some have recommended avoidance of extended-release formulations in patients who have undergone RYGB [215], though others have challenged the necessity of this practice. If an immediate-release formulation if available, the medications are commonly converted from extended-release to immediate-release [204]. If an immediate-release formulation is not available, consulting with a pharmacist to consider alternative formulations is often helpful. Ultimately, if a bioequivalent formulation better suited for a given patient is unavailable, a decision must be made whether to switch to another agent or to continue on the extended-release agent with close monitoring [203]. Ideally, these changes should be made months before the surgery. A third enteral alternative is orodispersible tablets, which disintegrate or partially dissolve in the mouth. It is important to note that orodispersable medications are not necessarily absorbed through the oral mucosa (notable exceptions include buprenorphine as in suboxone or oral nicotine replacement options such as lozenges or gum, which are transmucosally absorbed), and whereas they may optimize absorption by enhancing disintegration and dissolution, they still require a functioning GI system to be absorbed [203]. A fourth enteral option includes liquid formulations, which may enhance absorption as they do not require mechanical disintegration and dissolution. As there are many variables affecting the absorption of medications, parenteral agents continue to be a reliable method of medication administration where enteral absorption is compromised. Also it is judicious to obtain individual drug level when feasible.

General recommendations for medication management in WLS candidates:

- Review all psychotropic medications before bariatric surgery.
- Inform the patient about the potential changes in medication absorption.
- Educate both patients and their providers to monitor for signs of medication ineffectiveness due to malabsorption or toxicity.
- If relevant, obtain baseline medication level preoperatively.
- When applicable, regularly monitor medication blood level postoperatively.
- Consider performing a baseline presurgical symptom assessment using a formal rating scale specific to the patient's psychiatric disorder.
- Prior to the surgery, change the medication to an immediate-release formulation, or if this is not available, consult with pharmacy, or consider changing medication to an alternative, also consider parenteral formulation (e.g., haloperidol decanoate versus oral formulation).

As absorption typically normalizes around 1 year after WLS, one may consider resuming the original extended formulation regimen to minimize medication burden and side effects.

Summary

WLS candidates have a high prevalence of psychiatric disorders which, if left untreated, may impact postsurgical outcomes and decrease the health-related quality of life of patients undergoing the surgery. The presurgical psychosocial evaluation is an opportunity to identify the psychiatric conditions that need to be addressed and the psychological traits that may impact postsurgical course. As expected, eating disorders deserve careful attention in this setting. A history or a presence of psychiatric conditions, including symptoms of eating disorders, should not automatically exclude patients from WLS. It is important to ensure that the patient understands and is able to participate in all the lifestyle changes expected postsurgery. In the postsurgical setting, the treatment of psychiatric conditions needs to be adjusted according to the modifications in absorption, distribution, metabolism, and excretion that follow this life-changing intervention.

Take-Home Points

1. The presurgical psychosocial evaluation for WLS provides a tool to optimize the surgical outcome. The evaluation should capitalize on patient's strengths and work on eliminating or ameliorating patient's weaknesses.
2. The mere presence of psychiatric diagnoses is not necessarily a contraindication for WLS. Rather, the severity of symptoms and how the symptoms affect the patient's ability to adhere with recommendations are more valuable.
3. AUD can occur de novo in patients who have had no history of AUD. Thus, the utilization of screening tools for AUD in post-WLS patients is important.
4. Special attention should be given to medication dosing post-WLS as significant changes in pharmacokinetics occur, leading to potential toxicity or decreased therapeutic effect following WLS.

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13 Aesthetic/Cosmetic Surgery and Psychiatry

Ulas M. Camsari and Sheila G. Jowsey-Gregoire

Introduction

According to the American Society for Aesthetic Plastic Surgery, there were over 11 million surgical and nonsurgical cosmetic procedures performed in the USA in 2013. Among these, 16.5% were surgical procedures. From 2012 to 2013, there was a 6.5% increase in cosmetic procedures. The most common of these surgeries was liposuction and the second most common breast augmentation. Blepharoplasty, abdominoplasty, rhinoplasty, labiaplasty, and buttock augmentation were among other common procedures. Women had more than 10.3 million cosmetic procedures, which comprised 90.6% of all such procedures, whereas men had about 1 million procedures. People age 35–50 had the most procedures, accounting for 42% of the total. The most common surgical procedure also varies by age: the most common surgical procedure for people age 18 and under was otoplasty, ages 19–34 breast augmentation, ages 35–64 liposuction, and age 65 and over facelift. Racial and ethnic minorities had approximately 22% of all cosmetic procedures [1].

The American Board of Cosmetic Surgery uses the term "cosmetic" synonymously with "aesthetic" and defines cosmetic/aesthetic surgery as a discipline of medicine focused on enhancing appearance through medical and surgical techniques. Because cosmetic surgery is defined by enhancing a patient's appearance, its main goal is to improve aesthetic appeal, which often involves refining symmetry and proportion. Cosmetic surgery can be performed on all visible areas, including the head, neck, and body. It is practiced by doctors from a variety of medical fields, including plastic surgery, and aims to correct undesirable features of the body by reconstruction. Because cosmetic surgery is elective and does not aim to correct organ dysfunction, surgical indications are largely subjective, and the success of a procedure is measured by patient satisfaction [2]. Because psychiatric issues could influence one's self-image and motivation for surgery, preoperative psychiatric screening is essential [3].

Psychiatric aspects in a cosmetic surgery patient have been an academic area of interest since 1934. Menninger and Updegraff advocated for the importance of a psychiatric evaluation as part of the initial surgical assessment. Specifically, they emphasized importance of exploring the patient's motivations for operation and the effect of a patient's motivations on surgical success [4]. Publications from the 1950s focused on nasal plastic operations [5–7], and these early articles discussed psychological assessments using psychodynamic and psychoanalytic frameworks

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relying principally on the theories of Freud and Schilder [8]. Indeed, Schilder was the first to describe "psychological body image." The scarce literature based on psychodynamic approaches at that time described that feelings of inferiority or sexual inadequacy could be the primary motivation for seeking cosmetic surgery, and Meerloo argued that such a population should be excluded from surgical intervention [9]. In 1960, Clarkson and Stafford-Clark called for a classification of cosmetic surgery based on a patient's psychiatric presentation, and they described two different groups of cosmetic surgery patients who had either nonpsychotic or psychotic reactions to their disfigurements [10]. In addition to Menninger's 1935 description of "polysurgical addiction" [11], Knorr et al. described the "insatiable" cosmetic surgery patient in 1967 and recommended comprehensive management for these patients that involved collaboration between the psychiatrist and plastic surgeon [12].

Impact of Psychiatric Symptoms on Surgical Motivations and Clinical Outcomes

By definition, indications for cosmetic surgery are subjective, and all procedures are elective and voluntary, with the intent to change the appearance of the structure in question. Reported motivations and attitudes of cosmetic surgery candidates are, in most cases, individual-specific, e.g., coping with the past and with change, reconciling conflicting identities, finding or regaining a positive self-image, altering the way others look at oneself, defining self in relation to others, and pleasing others or self [13]. Hence, patient selection process of cosmetic surgery is different from other surgical disciplines, and outcome measurement is heavily focused on patient satisfaction, defined as patient-reported outcomes (PROs) and assessed by patient-reported outcome measures (PROMs). The Federal Drug Administration (FDA) defines a PRO as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else." Questionnaires are the most common form of PROMs, and both validity and suitability are the two most important elements in choosing the correct tool [14, 15].

In the early literature, most of the aesthetic surgery seekers were regarded to have some type of psychopathology explained by psychodynamic theories. Some even took a position against operating on a patient with psychopathology [9]. Several decades of additional literature provides more evidence that psychopathology is certainly more prevalent in cosmetic surgery patients; however, when it exists, it is not necessarily considered a contraindication. To the contrary, more recent studies have suggested that the potential for therapeutic value of cosmetic surgery from a psychiatric point of view should also be considered, such as improvement in general appearance satisfaction, positive long-term effects on appearance-related variables, and improved self-esteem [16–21]. Nevertheless, detailed psychiatric assessment is required preoperatively when psychopathology is suspected. The higher prevalence of mental illness in this surgical population calls for healthy collaboration between plastic surgeons and mental health professionals to address this need, which has been all the more pressing as plastic surgery has rapidly developed as a field [3]. Because surgical indication is based on subjective criteria, identification of psychopathology is essential to ensure clarity of shared expectations between surgeon and patient and also that psychological factors will not compromise surgical outcome as measured principally by patient satisfaction.

In a 2015 review by Herruer et al., predictive factors for dissatisfaction among facial surgery patients included male sex, young age, unrealistic expectations, minimal deformities, demanding patients, relational or familial disturbances, and either an obsessive-compulsive or narcissistic personality [22]. Psychological factors such as disturbed body image, low self-esteem, and depressive symptoms have been identified as predominant determinants of surgical success among patients undergoing rhinoplasty, even more so than achievement of facial aesthetic proportions [23]. Interestingly, Zojaji et al. reported that preoperative depression is positively correlated with postsurgical satisfaction [24].

Most cosmetic surgery psychological evaluations include a screening procedure as an initial step in which a wide range of different questionnaires are used to measure primarily psychiatric conditions or symptoms, to determine the need for psychiatric evaluation [25]. Several screening instruments to detect body image problems and body dysmorphic disorder (BDD) for various cosmetic surgical presentations have been developed [26–34], and routine screening for BDD is recommended particularly in certain types of cosmetic surgeries such as rhinoplasty [35]. Among commonly used scales are the Yale-Brown Obsessive Compulsive Scale (BDD-YBOCS) and Body Dysmorphic Disorder Questionnaire (BDDQ), both developed by Phillips et al. [30, 36]. The Body Dysmorphic Disorder Questionnaire Dermatology Version (BDDQ-DV) is a modified form of the BDDQ developed for use in cosmetic dermatology settings [37]. The Dysmorphic Concern Questionnaire (DCQ) was developed by Oosthuizen et al. [34], and the Body Dysmorphic Disorder Symptom Scale (BDDS or PISA Scale) was developed at the University of Pisa [32]. According to a systematic review in 2011, BDDQ-DV and DCQ were both reported to be the most suitable for further research on prevalence of BDD in cosmetic surgery and the impact of BDD on treatment outcome [32]. A more recent tool, the Cosmetic Procedure Screening (COPS) questionnaire, was developed by Veale et al. [27].

Screening and diagnosis for personality disorders can be challenging and often requires multiple assessments over an extended period of time. Although the prevalence of preoperative personality pathology among cosmetic surgery seekers remains unclear, personality disorders and maladaptive personality traits appear to be common in cosmetic surgery patients [38–42]. The Minnesota Multiphasic Personality Inventory (MMPI) is the most commonly used standardized personality assessment tool in this population [43–45]. Among the personality disorders, most commonly identified are narcissistic, obsessive-compulsive, borderline, and histrionic personality disorders. The research literature is scarce on the importance of the personality disorders in cosmetic settings. However, there are certain findings worth noting. Patients with borderline personality disorder have been generally regarded as very poor candidates for cosmetic surgery, and some consider this disorder a contraindication for cosmetic surgery. Two consistently identified concerns among these patient populations are the risk of self-injury and insatiable requests for aesthetic procedures [11, 12, 38, 46–51]. Similarly, Thompson et al. suggest that paranoid and histrionic traits predict poorer prognosis after cosmetic surgery [50].

Mental Health Screening Tools for Cosmetic Surgery

Several screening tools to assess general psychosocial functioning of cosmetic surgery candidates have been developed [3, 52–55] (see Table 13.1). Among these, Honigman et al. developed a psychosocial screen (PreFACE) for cosmetic face

Table 13.1 Screening instruments for cosmetic surgery candidates

Screening for BDD
Body Dysmorphic Disorder Questionnaire (BDDQ)
Dysmorphic Concern Questionnaire (DCQ)
Body Dysmorphic Disorder Symptom Scale (BDDS or PISA Scale)
Body Dysmorphic Disorder Questionnaire Dermatology Version (BDDQ-DV)
Psychosocial screen for facial surgery
PreFACE
Prime-D
Measure of psychological distress due to appearance
Derriford Appearance Scale (DAS59)
Psychosocial screen for cosmetic surgery
Cosmetic Procedure Screening (COPS)
Preoperative cosmetic suicidal risk screening
Detailed Assessment of Posttraumatic Stress (DAPS)

surgery candidates [52], which borrows items from a variety of other validated scales [25]. Prime-D is another scale developed at New York State Psychiatric Institute to detect psychiatric disorders in facial plastic surgery patients [53]. The Derriford Appearance Scale (DAS59) is a general psychometric scale which has been developed in the UK to measure the psychological distress caused by disfigurements, deformities, and aesthetic problems of appearance [55].

Body Dysmorphic Disorder in Cosmetic Surgery

Body dysmorphic disorder (BDD), formerly dysmorphophobia, is characterized by a preoccupation with one or more perceived defects or flaws in one's physical appearance. It is now classified within the category of obsessive-compulsive and related disorders in the *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition* [56]. BDD is the best described psychiatric disorder among cosmetic surgery patients. According to a 2017 meta-analysis, approximately 15% of plastic surgery patients have BDD. The mean age of a patient with BDD was 34 years, and women represented 74.3% of cases. Among dermatology patients, 12.7% had BDD, and the mean age of this subset of patients was 27 with females comprising 76% [57]. For comparison, the point prevalence of BDD in general population according to *DSM-5* is 2.4% (2.5% in women and 2.2% in men), whereas a lower prevalence has been reported outside the USA. Among cosmetic surgery seekers, BDD has been reported to be within a range of 2.2–56.7%. *DSM-5* reports a prevalence of 7–8% among US cosmetic surgery patients compared to 3–16% among international cosmetic surgery patients. BDD is the only *DSM-5* diagnosis that directly concerns body image [57].

Patients with BDD frequently present to cosmetic surgeons for corrections of minor, or in some cases nonexistent, defects. Whether BDD should be a contraindication for cosmetic surgery procedures has been debated for decades. Several studies have suggested that cosmetic treatments in the setting of BDD are associated with poor outcomes [58–63]; however, more recent studies and reviews have begun to suggest that cosmetic surgery may improve quality of life for patients with mild to moderate BDD [61, 64–67]. The weight of available evidence and current consensus both generally suggest a poor outcome for severe forms of BDD. For this population with severe body image distortion, nonsurgical psychiatric treatments such as cognitive behavioral therapy are recommended [12, 20, 61, 68–70].

Recognition of BDD in a surgical setting remains a challenge. A national survey completed among the members of the American Society for Aesthetic Plastic Surgery (ASAPS) in 2002 found that 84% of the aesthetic surgeons would refuse to operate on an individual with BDD [71]. Respondents, though, indicated they believed only 2% of patients seen for an initial cosmetic surgery consultation suffer from BDD, which represented a gross underestimation [71, 72]. A similar survey was completed in 2015 among members of the American Society for Dermatologic Surgery where 62% of respondents indicated they would refuse to provide a cosmetic procedure to a patient believed to have BDD [72]. Other European studies and reviews have also demonstrated that individuals with BDD present in different surgical settings and BDD are poorly identified by surgeons [26, 73–76].

BDD is associated with poor quality of life as well as increased suicide risk in children, adolescents, and adults. Approximately 80% of individuals with BDD reported past or current suicidal ideation, and about 25% have attempted suicide [77]. There are currently no medications approved by the FDA for the treatment of BDD. SSRIs are the usually recommended first-line pharmacological options based on limited evidence [78–80]. Published data are all but nonexistent on use of SNRIs and antipsychotics. Cognitive behavioral therapy has been shown to be effective [68]. Overall, treatment of BDD is a realistic goal, and patients should be offered assertive treatment to improve symptoms, functioning, and overall quality of life.

Depression and Suicidality Among Cosmetic Surgery Patients

Suicidality among cosmetic surgery patients has received attention, especially among those who seek breast augmentation [81]. In 2007, Sarwer et al. authored a review of six previous observational studies and found that suicide rates among women who received breast implants were roughly twice the rate expected based on data from the general population, though a causal relationship could not be assessed [82]. Additional studies in this population have revealed higher divorce rates, significantly lower body mass index, higher rate of psychiatric hospitalization [83], higher rates of major depressive disorder and antidepressant medication use [84], higher rates of alcohol use [85], and higher rates of tobacco use [84, 86].

BDD, being so common in cosmetic surgery patients, has received particular attention as a risk factor, since in general population it is independently associated with increased risk of suicide [77, 87]. Depression, shame [88], and anxiety [89] are considered the mediators between BDD and suicidal behavior. Therefore, preoperative screening of suicidality and depression is critical for identifying high-risk populations, and as such routine preoperative screening has been recommended by some [17]. The commonly used instrument to assess for depression and suicidal thoughts in this population is the Patient Health Questionnaire 9 (PHQ-9) [90]. In addition, several authors have proposed the Detailed Assessment of Posttraumatic Stress (DAPS) screen for preoperative cosmetic suicidal risk assessment [81, 91]. Detection of suicidality and/or depression should be an integral part of preoperative assessment, and a positive screen warrants comprehensive psychiatric consultation.

Other Psychiatric Conditions Among Cosmetic Surgery Patients

In 1993 as part of a comprehensive study of personality disorders among plastic surgery patients, Napoleon et al. reported 25% prevalence of narcissistic personality, 12% dependent personality, 9.5% histrionic personality, 9% borderline personality, and 4% obsessive-compulsive personality [38]. Two decades later, Dakanalis et al. independently reported high prevalence of personality disorders in this population: 18.9% had at least one personality disorder, with cluster B[1] and C[2] personality disorders predominating [39]. Also in this population, Vargel and Ulusahin reported a high level of depression and near-psychotic level of somatization [92]. A separate study found a 51% prevalence of psychiatric concerns among cosmetic surgery candidates and identified trait interpersonal sensitivity as the most common condition and psychosis the least common [40].

Specifically among rhinoplasty seekers, Zojaji et al. reported that obsessive-compulsive, dependent, histrionic, and narcissistic personality disorders were common, but narcissistic personality was the most common [24, 41]. Similarly among rhinoplasty seekers, Naraghi and Atari reported higher prevalence of depression and obsessive-compulsive disorder, along with a higher prevalence of interpersonal problems, psychoticism, paranoia, phobia, and hostility [94, 95].

Higher prevalence of substance use, particularly tobacco and alcohol, has been identified in cosmetic surgery candidates. The risk of substance use in this population goes beyond mental health sequelae. In fact, a 2016 meta-analysis revealed a heightened risk of cutaneous necrosis, particularly in the event of major detachment (e.g., cervico-facial lift, skin-sparing mastectomy, abdominoplasty), delayed wound healing, and surgical site infections in patients with substance use disorders [96].

Several studies have also explored the relationship between eating disorders and cosmetic

[1] *Cluster B personality disorders* are characterized by poor impulse control and emotional dysregulation. They include *borderline personality disorder*, *narcissistic personality disorder*, *histrionic personality disorder*, and *antisocial personality disorder* [93].

[2] *Cluster C personality disorders* are characterized by anxious, fearful thinking or behavior. They include avoidant *personality disorder*, *dependent personality disorder*, and *obsessive-compulsive personality disorder* [93].

surgery. A purging diagnosis has been associated with a favorable attitude toward cosmetic surgery seeking, and a history of cosmetic surgery was associated with diagnosis of an eating disorder [97, 98]. Interestingly, aesthetic liposuction and abdominoplasty were reported to reduce the overall risk for an eating disorder significantly and improve overall body satisfaction [99, 100].

Overall, the evidence on psychiatric outcomes after cosmetic surgery are mixed. A critical review of the literature on psychological outcomes among women suggests that whereas cosmetic surgery may improve satisfaction with specific body parts, overall body image does not appear to be enhanced substantially by surgery [101]. Indeed, more than half of women undergo a second procedure. Though interpersonal relationships may improve for select individuals, the weight of the evidence suggests that women should not expect cosmetic surgery to enhance relationships. To the contrary, BDD and unrealistic expectations of cosmetic outcomes both portend dissatisfaction with outcomes and a worsening of overall sense of well-being.

Psychological Management in the Plastic Surgery Setting

The literature on psychiatric interventions unique to the cosmetic surgery patient remains in its infancy though common themes for general psychiatric management of the surgical patient apply. In the perioperative setting, the main task is to screen for most common psychiatric diseases and establish if the patient has the ability to provide informed consent. For instance, where a patient has an established outpatient mental health provider, such treating providers should be contacted as part of the preoperative assessment for surgery. Family involvement should be solicited. Because cosmetic surgery patients may undergo repeated procedures, records from previous surgeons should be obtained to understand the nature of a patient's relationship with care and to understand more fully their cosmetic expectations. Previous records may reveal "red flags" such as excessive requests for cosmetic surgeries or procedures, dissatisfaction with the results of prior surgery not correlated with the objective outcome, camouflaging behavior, demanding behavior toward the surgeon or staff, unrealistic expectations especially expectation that the cosmetic procedure will be the solution to problems in other areas of life, and thinking that others are equally disturbed with the defects [76].

When psychiatric disorder is suspected or the capacity to provide informed consent is questionable, formal psychiatric evaluation and referral for treatment should be encouraged. For patients with preexisting psychiatric problems who undergo cosmetic surgery, there is no literature on specific psychiatric interventions to be implemented in the perioperative settings. General principles of care as outlined in 2, 3, 4, and 5 can be adapted to serve the individual needs of the patient.

Vascularized Composite Allotransplantation

One final related topic is that of hand and face transplantation, which have obvious cosmetic implications. This surgery involves transplantation of a vascularized composite allograft (VCA) from a deceased donor to a patient with limb loss or facial disfigurement. Close to 100 hand transplants and approximately 35 face transplants have occurred as of 2018 [102, 103]. No specific rating scale has been designed to assess these patients' psychosocial functioning specifically, but a consensus is emerging about the key domains for the psychosocial assessment, which we discuss below [104, 105].

As with solid organ transplant patients, the preoperative evaluation for hand or face transplantation should include assessment for psychiatric disorders, family support and availability, adherence history, knowledge about transplantation, motivations for transplant, and history of alcohol, drug, or tobacco use. Because individuals experience limb loss or facial disfigurement due to trauma, screening for posttraumatic stress disorder should also be included in the evaluation. Additionally for this population, assessment of a patient's expectations for transplantation, ability to adhere to lengthy rehabilitation, appreciation of anticipated early postoperative lack of function, and potential for media interest have also been recommended.

Education about posttransplant psychiatric side effects of immunosuppressant medications including insomnia, mood changes, and tremor is important to help patients understand the potential from a psychiatric perspective that they will be exposed to with transplantation. In addition to functional improvements, issues related to body image, social isolation, and social ostracism are important factors in motivating patients and will be important for improved quality of life following transplantation.

Summary

The widespread Western interest in body image combined with an increasing shift from principally reconstructive plastic surgery to purely cosmetic applications implies an important role for psychiatric care among this population. As bioethicists continue to work through the difficult distinctions between "therapy" and "enhancement" as well as the role of medicine in this arena [106], cosmetic surgery remains widely available, and this calls for careful consideration of the mental health aspects of this surgical population to optimize outcomes.

Take-Home Points

1. All cosmetic procedures are elective because all the visible organs are functionally intact; therefore, surgical indications are subjective.
2. The success of a procedure is measured by patient satisfaction ("patient-reported outcomes), which makes preoperative psychiatric screening essential.
3. Body dysmorphic disorder is the most common psychiatric disorder among cosmetic surgery patients and associated with poor outcomes. Despite this, it is broadly under-recognized by plastic surgeons and dermatologists.
   - Cosmetic surgery candidates have higher prevalence of substance use—particularly tobacco and alcohol—than the general population. Cosmetic surgery patients are also at significantly increased risk of depression and suicide, especially those with body dysmorphic disorder and patients undergoing breast augmentation.
4. In some instances, cosmetic surgery may improve the psychological status of the patients (e.g., liposuction and binge eating).

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14 Psychiatric Aspects of Obstetrics and Gynecology Patients

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Introduction

Gynecology is the medical and surgical specialty focusing on the care of women throughout their lifespan. A gynecologist must appreciate the hormonal, social, cultural, and psychological issues that accompany gynecological conditions. Gynecologic surgery may be performed to improve quality of life by relieving symptoms (e.g., such as dysfunctional bleeding) or may be life prolonging, such as surgery for gynecologic cancer. Psychiatric conditions such as depression and anxiety often influence gynecologic conditions and their surgical outcomes. Conversely, the implications of gynecologic disorders and surgery are intimately tied to body image, femininity, and sexuality, which can affect psychiatric conditions and quality of life.

In the last 30 years, the number of hospital-based gynecologic surgeries including hysterectomy has decreased [1–3]. This trend reflects changes in women's attitudes toward body integrity, the increased use of minimally invasive surgery including robotic and laparoscopic surgery, and the shift from inpatient to ambulatory and office settings [3–5]. As the US population ages, the annual number of women undergoing surgery for malignancy, urinary dysfunction, and pelvic organ prolapse is expected to increase.

Psychiatric presentations in surgical gynecologic patients may be related to pre-existing or de novo psychiatric presentations. Pre-existing psychiatric conditions can predispose patients to gynecologic problems through direct biological impact or through high-risk behaviors (e.g., anorexia and amenorrhea, promiscuity related to substance abuse, and risk of HPV and cervical cancer). Other psychiatric diseases such as depression or schizophrenia can co-occur in parallel and impact gynecologic disease indirectly, mainly through difficulties with adherence with screening or medical care. Finally, some psychiatric presentation may start around the time of gynecologic surgery as a direct complication (e.g., delirium, pain disorders) or an expression of psychological adjustment (adjustment disorders). Many prevalence studies, however, measure psychiatric symptoms only without establishing a definite psychiatric diagnosis; therefore, they may not differentiate between primary psychiatric conditions and adjustment disorders in reaction to the medical illness or the surgical event.

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Psychiatric Aspects of Common Gynecologic Surgeries

Hysterectomy

Approximately 600,000 women in the USA have a hysterectomy each year [6]. Despite the decrease in the number of annual hysterectomies performed over the last three decades, it remains the second most common surgical procedure among women in the USA [3]. Ninety to 95 percent of hysterectomies are performed due to benign indications such as leiomyoma, dysfunctional uterine bleeding, and pain [7, 8]. Hysterectomy is also a part of gynecologic cancer treatment. While earlier retrospective studies reported an association between hysterectomy and adverse psychological sequelae, prospective studies have failed to confirm these findings. Studies on the psychological effects of hysterectomy are heterogeneous in terms of standardized assessment tools, indications for hysterectomy, menopausal status, and ovarian conservation [9]. In one prospective cohort study of perimenopausal women, depressive affect was not predictive of hysterectomy [10]. The incidence of depression prior to hysterectomy is also greatly affected by the impending surgery, associated anxiety, and gynecological symptoms. Women who had hysterectomies for non-cancer indication had improved quality of life and reduction in psychiatric symptoms after hysterectomy [11, 12]. Pain and sexual functioning also tend to improve after hysterectomy [13, 14]. However, younger women or women with gynecologic cancer have been shown to have more severe psychologic symptoms after hysterectomy compared to older women and those without cancer [15].

Pelvic Exenteration

For some patients with advanced gynecologic cancers, most commonly cervical cancer, pelvic exenteration is a life-prolonging or life-saving procedure that includes removal of pelvic organs including the uterus, cervix, vagina, bladder, and rectum. Since pelvic exenteration was first described in 1948, perioperative mortality from pelvic exenteration has decreased from 23% to 3–5% with advancements in preoperative preparation, imaging techniques, intraoperative monitoring, surgical techniques, and postoperative care [16, 17]. The extensive nature of this surgery directly affects physical and sexual function, body integrity and image, and quality of life of women undergoing pelvic exenteration. In one study of 47 women undergoing pelvic exenteration, 40% had significant distress based on Psychological Distress Inventory (PDI) when evaluated during the preoperative period [18].

Sterilization

For married couples, sterilization (including male and female) is the most prevalent method of contraception [19]. Most commonly, female sterilization is achieved by occluding the fallopian tubes, which is considered to be permanent. Given history of sterilization on women without consent or knowledge and women who were denied sterilization, the American College of Obstetricians and Gynecologists (ACOG) recommends respecting a woman's autonomy for undesired fertility with obstetrician-gynecologists providing pre-sterilization counseling [19]. Women should be offered long-acting reversible contraceptive methods such as intrauterine device. In a prospective, multicenter study following 11,232 US women aged between 18 and 44 years for up to 14 years, up to 14% of women after sterilization requested information about reversal [20, 21]. Women aged 30 years or younger were likely to express regret than those older than 30 years (20.3% vs 5.9%) [20]. A systemic review shows that younger age is consistently associated with regret [22]. In a telephone-based survey of US women who underwent sterilization, women who reported more depressive symptoms were more likely to endorse regret [23]. Despite these evidences, ACOG states that a young woman requesting sterilization should not trigger an automatic psychological evaluation [19]. However, if the decision seems to be based on psychological distress, a psychological evaluation should take place before sterilization.

Dilatation and Curettage and Termination

Dilatation and curettage are the most common gynecologic procedures with multiple indications including workup or treatment of abnormal uterine bleeding, termination of pregnancy, or completion of spontaneous abortion (a lost pregnancy before 20 weeks). Since there is limited literature on psychiatric aspect of dilatation and curettage for abnormal uterine bleeding, the following section will focus on dilatation and curettage for obstetrical indications.

It is generally expected that women who suffer from unwanted loss of pregnancy experience sadness, but increase in anxiety and depressive symptoms has been found 2 years after pregnancy loss [24, 25]. Factors that increase the risk of psychological consequences after a spontaneous abortion include a history of major depression, childlessness, high investment in the pregnancy, concerns regarding infertility, and lack of social support [26]. For the last eight decades, the mainstay treatment for spontaneous abortion has been dilatation and curettage. However, prostaglandins such as misoprostol now offer women with spontaneous abortion a nonsurgical option. A small randomized, controlled trial (n = 217) from Hong Kong showed that there was no significant difference in psychological outcomes at 2 weeks, 2 months, and 6 months [27].

Office Colposcopy and Cervical Biopsies

Abnormal cervical cancer screening based on cytology and human papillomavirus (HPV) is followed by office colposcopy, direct examination of the cervix under microscopy. Suspicious lesions can be removed during colposcopy by large loop excision of the transformation zone (LLETZ) or be biopsied only with the patient returning at a later time for treatment. Besides the fear of cancer, uncertainty about the procedure and concerns about pain contribute to pre-colposcopy anxiety [28]. Correlates contributing to pre-colposcopy anxiety include single status having children, pre-existing anxiety, depression, perception of long waiting time, and dissatisfaction with pre-colposcopy information [29]. However, there is no significant difference in pre-colposcopy anxiety in women who received information leaflet versus no information leaflet or informational leaflet, video and counseling versus informational leaflet and video without counseling [30]. A meta-analysis showed that music reduced anxiety and pain during colposcopy compared to no music [30]. Even after colposcopy, some women continue to experience anxiety. In 1 study of 584 Irish women attending colposcopy clinics, the prevalence of anxiety as measured by the Hospital Anxiety and Depression Scale (HADS) remained stable at 4, 8, and 12 months [31]. Non-Irish nationality, lack of private health insurance, history of depression, and lower satisfaction with life were associated with anxiety [31]. Specific anxiety in the form of worries about cervical cancer, fertility, and having sex declines over time but remains high at 12 months (23%, 39%, and 18%, respectively) [31].

Delirium and Post-Intensive Unit Care Syndrome

Postoperative delirium is a common complication after surgery. In the elderly, delirium is associated with longer hospital stays, institutional care, and mortality [32]. Gynecologic cancer and pelvic floor dysfunction are more common in older adults. In the past 40 years, the number of all gynecologic procedures fell except for incontinence procedures [1]. Approximately 17.5% of women undergoing major surgeries for gynecologic malignancies developed postoperative delirium [33]. Independent risk factors for delirium after surgeries for gynecologic malignancies include age, number of preoperative medications, and increased narcotic analgesics [33].

Many women who undergo surgery for gynecologic malignancy require care in an intensive care unit (ICU). Although most recover, many develop residual physical, cognitive, and psychiatric disabilities, which are elements of the post-intensive unit care syndrome (PICS) [34]. Risk factors for psychiatric features in PICS include ICU-dependent factors such as longer duration of sedation, mechanical ventilation, length of ICU stay, or restraint use and personal factors including premorbid psychiatric disease, female sex, and lower educational level [35]. Physical disability is predicted by corticosteroid use, longer time to physical rehabilitation, and persistence of medical conditions [35]. Delirium, premorbid cognitive status, and level of education are risk factors for long-term cognitive impairment [35].

Prehabilitation refers to interventions implemented before surgery in order to improve the general health status of the patient and optimize recovery. Many authors suggest that prehabilitation should include psychological evaluation and assistance, which may include screening, counseling for stress management, coping skills training, cognitive behavioral therapy, or other types of psychotherapy [36, 37]. Prehabilitation is being investigated to improve psychological and physical functioning preoperatively to minimize postoperative complications [37, 38]. Once a patient is admitted to the ICU, non-pharmacological interventions to decrease and treat pain, agitation, and delirium should be implemented [39]. Using screening tools such as the Confusion Assessment Method (CAM) for the ICU should be used to identify delirium [39]. Benzodiazepines, aside from managing alcohol or benzodiazepine withdrawal, are best avoided due to their potential for worsening delirium [39]. Early mobilization is recommended to prevent delirium and improve physical functioning [40]. The ICU is a chaotic environment and thoroughly disruptive to sleep. Noise and light at night should be minimized, and necessary direct patient care and procedures such as phlebotomy, measuring vital signs, and medication administration should be clustered overnight to minimize sleep disruption [34]. Antipsychotics in delirium are best reserved for the management of severe symptoms that place a patient or others at imminent risk of harm [41].

Prevalence of Psychiatric Conditions in Gynecologic Patients

Depression

A woman is 50% more likely than a man to suffer from a mood disorder during her life [42]. The lifetime prevalence of mood disorders in women is 20%, with major depressive disorder the most common of these conditions [42]. Major depressive disorder is defined by at least one 2-week episode of either depressed mood or loss of interest, accompanied by symptoms such as change in appetite, disrupted sleep, decreased energy, a feeling of worthlessness or guilt, poor concentration, psychomotor slowing or agitation, and recurrent thoughts of death or suicidal ideation [43]. As approximately one-third of women in the USA consider their obstetricians and gynecologists as their primary care physicians [44–46], gynecologists can play an important role in diagnosing depression. The majority of women with depression present to their gynecologists with physical symptoms, and only 11% patients present with psychologic complaints and another 30% with psychological distress [47]. Therefore, if depression is not screening routinely, then the diagnosis may be missed. In a study of 1013 women attending gynecologic clinics, the prevalence of depressive disorder based on the Primary Care Evaluation of Mental Disorders (PRIME-MD) was 27.2% [48]. In 2015, the American Congress of Obstetricians and Gynecologists (ACOG) recommended that depression screening should be included in a well-woman visit [49].

Uterine leiomyoma (commonly known as a uterine fibroid) is a benign tumor that affects many women. In fact, greater than 80% of African American women and up to 70% of Caucasian women in their 40s have uterine leiomyoma [50]. Symptomatic leiomyomas account for the main indication for hysterectomy [51]. Depending on the number, size, and location of the leiomyomata, women may experience a variety of symptoms including pain, urinary symptoms, menorrhagia, dysmenorrhea, and infertility. Depressed mood is common in patients with uterine leiomyoma [52]. In a large population-based study of women, the incidence of depression in women with uterine leiomyoma was 54% higher than those without leiomyoma, and incidence of depression improved for women who sought surgical intervention [53].

Endometriosis is found in 10–15% of women of reproductive age [54, 55]. It is characterized by the implantation of endometrial stroma and glands outside of the endometrium, and this condition of extrauterine tissue is associated with dyspareunia, dysmenorrhea, and infertility. The reported rate of depression in endometriosis varies widely across studies from 12.5% to 86.5%, due in large part to the small study samples [56–58]. The extent of endometriotic spread does not necessarily correlate with pain severity nor psychological distress. For instance, one study found that the prevalence of depression was significantly greater in women with endometriosis accompanied by chronic pelvic pain compared to those without pain (86–38%) [59].

Polycystic ovary syndrome (PCOS), found in 10% of reproductive-aged women, is characterized by androgen excess, ovulatory dysfunction, and polycystic ovaries and is commonly accompanied by metabolic dysfunction including insulin resistance [60, 61]. Clinically, PCOS manifests as menstrual irregularity, infertility, hirsutism, acne, obesity, and alopecia. In two large national population-based cohort studies, women with PCOS had a 1.25- to 2.3-fold increase risk of depression [61, 62]. Another national population-based study showed that women with PCOS also had a 1.3-fold increase in developing depression during the 10-year period [63].

Urinary incontinence can affect women of all ages with a lifetime prevalence of 15–53% [64–66]. Urinary incontinence is categorized as stress, urge, or mixed incontinence. Stress incontinence is defined as the loss of urine on physical exertion, sneezing, or coughing [67]. Urge incontinence is characterized by leakage accompanied by or preceded by a sudden urgency to urinate [68]. Mixed incontinence is a combination of stress and urge incontinences. The prevalence of urinary incontinence increases with age [66, 69, 70]. It has a negative impact on quality of life, often leading to social isolation. A woman has a lifetime risk of 13.6% of having a surgical procedure to improve symptoms of urinary incontinence [71]. In a cross-sectional study of 5701 women, aged 50–69 years, the severity of urinary incontinence was associated with a higher likelihood of depression—in fact, women with severe incontinence had twice the depression as those with mild to moderate urinary symptoms (80% vs 40%) [72].

Pelvic organ prolapse is the descent of the uterus and vagina, which is often associated with a sensation of a bulge or pressure. It can be accompanied by urinary, bowel, and sexual dysfunction. In a large cross-sectional study of women older than age 20 in the USA, the prevalence of symptomatic pelvic organ prolapse was 2.9% [73]. However, because most women with this condition are asymptomatic, its true prevalence based on systematic examination may be as high as 41–50% [74]. Many women who are symptomatic will seek treatment, with the lifetime risk of surgery for pelvic organ prolapse being 12.6% [71]. In one study of women seeking surgery, 22% of the women had moderate to severe depressive symptoms [75]. When compared to the control group of women in the general gynecology clinic, women with pelvic prolapse were five times more likely to have depressive symptoms [75]. The severity of symptoms related to prolapse was also predictive of depressive symptoms [75].

The most common forms of gynecological cancers categorized by organ of involvement are endometrial, cervical, ovarian, vaginal, and vulvar cancer. In 2017, an estimated 107,500 new cases of gynecologic cancer will be diagnosed in the USA [76]. Endometrial cancer is the most common gynecologic cancer with an anticipated 61,500 new cases in 2017, followed by ovarian (22,400 cases) and cervical cancer (13,000 cases) [76]. Vulvar and vaginal are less common with an anticipated 6000 and 5000 new cases, respectively [76]. Women with gynecologic cancer have significant psychological distress [77]. Rates of depression reported in this group vary due to the methodology and diagnostic criteria used. The association between premorbid depression and cancer remains unclear; however, a growing body of evidence suggests that depression may influence cancer progression [78].

Endometrial cancer is localized disease when diagnosed in 67% of cases, and the overall 5-year survival rate is favorable at 82% [76]. In a South Korean population cohort study, premorbid depression was not found to be associated with increased risk of endometrial cancer [79]. Conversely, a population cohort study from Taiwan found that women with endometrial cancer did not have a higher risk for developing depression [80]. However, when the Taiwanese women were stratified into different age groups, younger women with endometrial cancer had an elevated risk of developing depression [80].

Cervical cancer incidence in the USA has decreased by more than 50% since the introduction of widespread cervical cancer screening and vaccine programs to prevent infection with oncogenic strains of human papillomavirus (HPV) [81]. In fact, vaccination has been shown to prevent up to 70% of HPV infections, which are responsible for most cervical cancer [82]. Even still, cervical cancer remains the most commonly diagnosed gynecologic cancer worldwide [83]. The prevalence of depression in women with cervical cancer ranges widely based on the nature of the study, from 7% to 50% [84, 85].

Ovarian cancer, unlike cervical and endometrial cancers, does not have a screening test and often presents without symptoms until disease is advanced. As a result, 70–75% cases of ovarian cancer are diagnosed in advanced stages [86]. The overall 5-year survival in advanced-stage ovarian cancer is 20–30% [86]. A meta-analysis revealed that the prevalence of depression in women with ovarian cancer before treatment, during treatment, and after treatment were 25%, 23%, and 13%, respectively [87]. Drawing from two large prospective US cohorts, women diagnosed with depression 2–4 years before cancer diagnosis were found to have a 1.3-fold increased risk for ovarian cancer [88].

Hormonal contraceptives are commonly prescribed for benign gynecologic conditions in addition to being prescribed for birth control. Up to 10% of women on oral contraceptives report depressive symptoms, and these symptoms often lead to medication discontinuation [89–91]. A large cohort trial in women on hormonal contraceptives was shown to have higher risks of subsequent antidepressant prescriptions and depression diagnoses [92]. The risk of antidepressant exposure among these women generally decreased with age, with adolescents having the highest risk [92]. A recent randomized, controlled trial did not find a consistent relationship between oral contraceptives and depression, but women who received an oral contraceptive did report reduced overall well-being [93].

Bipolar Disorder

The lifetime prevalence of bipolar spectrum disorder is 3.9% [42]. Bipolar I disorder is defined by the lifetime presence of at least one manic episode, though nearly all patients with this condition have major depressive episodes as well. Bipolar II disorder is defined by at least one hypomanic episode and a major depressive episode [43]. The criteria for manic episode include either markedly elevated or irritable mood for 1 week (or less if the episode requires psychiatric hospitalization), as well as accompanying symptoms such as decreased need for sleep, grandiosity, increased goal-directed activity, flight of ideas, distractibility, and poor judgment [43]. A hypomanic episode is characterized by the same symptoms as mania, with three slight distinctions: (1) compared to mania, hypomania causes less functional impairment; (2) unlike the week-long requirement of index symptoms for mania, hypomania is diagnosed after only 4 days of symptoms; and (3) psychotic symptoms are incompatible with hypomanic episode [43]. Bipolar I disorder affects men and women equally; however, women have a higher prevalence of bipolar II disorder [94]. Bipolar disorder also manifests differently in women. For instance, women are more likely to have rapid cycling (i.e., four or more mood episodes within a year), episodes with mixed features (i.e., concurrent features of mania and depression), and antidepressant-induced mania [95]. Research attempting to associate specific bipolar-related symptoms to each phase of the menstrual cycle remains inconclusive, despite the reports of many women of cyclical symptoms during menstrual cycles [96–99].

Endometriosis may be associated with bipolar disorder; however, evidence for this association has been inconsistent. For instance, one study found that 10 of 16 (63%) women with endometriosis had bipolar disorder [100]. A follow-up study found an 8% prevalence of bipolar disorder in women with endometriosis, compared to 4% in those without endometriosis [101]. Although the association between bipolar disorder and endometriosis remains speculative, women with this condition who are started on an antidepressant should be monitored closely for symptoms of mania or hypomania, which is especially important to keep in mind for this population because antidepressants are commonly used to treat pelvic pain.

Valproic acid has been implicated as the cause of PCOS in women with epilepsy, a fact that, in part, has led investigators to examine the relationship between PCOS and bipolar disorder [102]. In a study of 78 women with PCOS, 19 women (28%) had either screened positive for or had a previous diagnosis of bipolar, and only 2 of these women (3%) had previously been exposed to valproic acid [103]. A separate cohort study of 72 women with PCOS found similarly in that 8 women (11.1%) were diagnosed with bipolar disorder [104]. Evidence for an association between PCOS and bipolar disorder has not been replicated in large population cohort studies. In one such study among Taiwanese women ($n = 5341$), those with PCOS were not found to have an increased risk of bipolar disorder [63]. However, in a Swedish cohort of 24,385 women with PCOS, women with PCOS were found to have 1.4 times risk of bipolar disorder when adjusted for comorbid psychiatric disorders [62].

Anxiety Disorders

Anxiety disorders are the most prevalent classes of psychiatric disorders, with a lifetime prevalence of 28.8% [42]. Women are 60% more likely to have an anxiety disorder than men [42]. Anxiety disorders include generalized anxiety disorder, panic disorder, social phobia, and specific phobias. Especially relevant for gynecologic practice, which commonly involves surgical intervention, the perioperative period represents a time of enhanced vulnerability to anxiety. When anxiety is examined in gynecologic conditions, researchers use heterogeneous definitions and criteria making prevalence and incidence difficult to compare. Therefore, whenever possible, descriptions of how anxiety is measured or defined are included in the following sections examining anxiety and gynecologic conditions.

Pain and anxiety are intimately related. One would expect a find a close association between anxiety and conditions known to cause significant pain such as endometriosis. In a prospective study with 104 women with endometriosis, the rate of anxiety symptom was 87.5% based on the Spielberger State-Trait Anxiety Inventory (STAI) and the Hamilton Rating Scale for Anxiety (HAM-A) [56]. Pain intensity was also highly correlated with STAI and HAM-A scores [56]. Although anxiety symptoms appear to be common, the prevalence of anxiety disorders in endometriosis has not been well studied. In a systematic review of 18 quantitative studies that examined psychiatric diagnoses in women with endometriosis, only 3 studies used control groups for comparisons and clinical diagnostic criteria for diagnosis [105]. Of the 78 women with endometriosis in these 3 studies, 12.8% were diagnosed with anxiety disorders [105]. Endometriosis has been associated with 1.44 times the risk of developing an anxiety disorder relative to those without the condition, based on a study based on data from a large national database, and again the severity of anxiety correlated with the intensity of pain [106].

Anxiety is common in patients with PCOS. In a meta-analysis, women with PCOS were found to have substantially higher prevalence of general anxiety symptoms than controls (20.4% vs 3.9%, odd ratio 6.88) [107]. In two separate cohort studies—one Swedish and the other Taiwanese—women with PCOS had a roughly 1.4-fold increased risk for any anxiety disorders than matched controls [62, 63].

Urinary incontinence is also associated with anxiety. A university study of urogynecology clinic patients (*n* = 218) evaluated patients using the Primary Care Evaluation of Mental Disorders (PRIME-MD) Patient Health Questionnaire (PHQ) and found an elevated prevalence of panic disorder among those with urge or mixed incontinence (11%) compared to those with stress incontinence (0%) [108]. The unpredictability of urge or mixed incontinence may account for the difference. One factor that appears to mediate the association between urinary incontinence and anxiety is whether a woman has associated functional impairment. This suggests that assertive management of functional impairment might have positive effects on anxiety in this population as well [109].

The prevalence of anxiety disorders in women with pelvic organ prolapse has received little attention. Qualitative research has found that women with this condition may fear “something being wrong” or having cancer [110]. In a cross-sectional study of 1510 women at a university pelvic care center, one in five women was found to have clinically significant anxiety [111]. Among women seeking weight-loss surgery, however, the prevalence of current or previous anxiety diagnosis was not significantly different between women with or without pelvic floor dysfunction [112].

The range of prevalence of anxiety in cervical cancer varies significantly as studies used different definitions for anxiety; however, in general cervical cancer engenders anxiety. Anxiety may be heightened when a woman is undergoing treatment for cervical cancer. For instance, the prevalence of anxiety using the Hospital Anxiety and Depression Scale (HADS) in a cross-sectional cohort of Chinese women with cervical cancer admitted as inpatients was 65.6% [85]. Stage of disease also influences anxiety prevalence: Italian women with locally advanced disease prior to treatment have been found to have a higher prevalence of anxiety than those with early disease (28% vs 9%, respectively) [113]. This study also used HADS for anxiety, but the authors used the cutoff of >11, while the Chinese study used a cutoff of >8. For survivors of cervical cancer, though, the overall prevalence of anxiety may be no higher than the general population according to a South Korean study (40% vs 32%, respectively) [114]. However, Korean women <50 years of age had more anxiety than women without history of cervical cancer of the same age group (40% vs 26.4%, respectively) [114]. Based on the Chinese-Bilingual Structured Clinical Interview for DSM-IV Axis I Disorders, the prevalence of anxiety disorders in a cohort of cervical cancer survivors in Hong Kong was 16%, and the most common anxiety disorder was generalized anxiety disorder [115].

In view of the poor prognosis associated with ovarian cancer, this diagnosis and even surgical intervention for suspected ovarian cancer, independent of final histopathological diagnosis, are closely associated with anxiety. In a study that enrolled women undergoing surgery for suspected ovarian cancer, Sukegawa showed that all patients scored high on Spielberger State-Trait Anxiety Inventory (STAI) before surgery; however, after pathology results were disclosed, STAI score decreased significantly in women with benign diagnosis, whereas anxiety remained elevated in the women diagnosed with cancer [116]. Further, a meta-analysis of women with ovarian cancer found that anxiety did not improve after treatment [87]. The prevalence of anxiety before, during, and after treatment were 19%, 26%, and 27%, respectively [87]. The authors suggested that this weak trend of increasing anxiety might be related to uncertainty among study participants regarding risk of disease recurrence.

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) occurs after experiencing or witnessing a horrifying, typically life-threatening event and is characterized by four clusters of symptoms: affective, re-experiencing symptoms, avoidance, and hyperarousal [43]. Approximately 50% of women in the USA will experience a traumatic event in their life [117]. Sexual trauma and childhood trauma are more common in women than men [118]. The lifetime prevalence of PTSD in the general population is 6.8% [42], and women have a higher lifetime prevalence than men (9.7% and 3.6%, respectively) [117]. Female veterans have been found to have an elevated lifetime prevalence of 26.9% [119]. Prior trauma, premorbid psychiatric disorders, family history of psychiatric disorder, perceived threat during trauma, posttraumatic emotional response, and absence of posttraumatic support are predictors for developing PTSD [120, 121]. Women with PTSD are also at risk for developing comorbid psychiatric conditions such as depression and anxiety [122]. Not only does trauma cause psychological distress and functional impairment, it also has a powerful effect on medical health. For instance, women with a history of sexual trauma will use more medical services and are at risk for a host of lifestyle diseases [123, 124].

Sexual assaults, accidents, and exposure to other violent events are most associated as the inciting event of PTSD. The experience of being diagnosed with cancer, receiving treatment for it, or dealing with its consequences can be severely traumatic, and as a result there is a growing body of research on PTSD in cancer patients. A meta-analysis revealed a 1.66-fold increase in risk of PTSD in cancer survivors relative to non-cancer controls, and approximately 13.2% of women with gynecologic cancer have PTSD [125]. In a prospective study of 121 women diagnosed with ovarian cancer, 57% fulfilled the diagnosis of PTSD at least once during or 3 months after treatment, and 13% had persistent symptoms throughout and 3 months after treatment [126].

Schizophrenia

Approximately 1% of the US adult population has schizophrenia. Men are more likely than women to develop schizophrenia with incidence risk ratio of 1.4 to 1 [127]. Women may develop schizophrenia later in life, and there is a second incidence peak in women around the time of menopause [128].

Data examining the relationship between PCOS and schizophrenia is scarce. In a Swedish cohort, 24,385 women with PCOS had a 1.26-fold increased risk for schizophrenia, and 25,921 full sibling of women with PCOS had 1.3-fold higher risk for schizophrenia [62], suggesting perhaps a shared genetic vulnerability for the two conditions. In contrast, a separate Taiwanese study of 5431 women was unable to find evidence that PCOS increased risk of schizophrenia diagnosis during 10 years of follow-up [63]. The divergent findings of these two populations may be due to the larger sample and longer study duration in the Swedish cohort.

Substance Use Disorders

The lifetime prevalences of alcohol use disorder and other substance use disorders in women are 19.5% [129] and 7.1% [130], respectively. Women have lower rates of illicit drug or substance use than men across all age groups [129]. However, women progress more quickly than men from initiation of substance use to substance use disorders [131]. By the time women enter treatment, they tend to have advanced medical, psychiatric, and social problems.

Alcohol increases serum estrogen level, which in turn affects menstrual cycles as well as several gynecological conditions. Alcohol increases serum estrogen levels by two primary mechanisms—inducing activity of aromatase, the enzyme that converts testosterone to estrogens, and influencing luteinizing hormone (LH), the hormone responsible for ovarian production of estradiol [132–136]. Substance use disorders may influence gynecological conditions either directly, through biological activity of the substance (e.g., alcohol and its impact on the endocrine system), or indirectly, through high-risk behaviors (e.g., IV drug use or risk of contracting sexually transmitted disease).

Eating Disorders

The lifetime prevalence of anorexia nervosa for women is 4%, for bulimia nervosa 2%, and for binge eating disorder 2% [137]. Obstetricians and gynecologists play an important role in recognizing and identifying eating disorders, as many women with eating disorders will present with gynecological consequences. Amenorrhea, irregularity menses, and infertility are common in patients with both anorexia and bulimia. Bulimia nervosa and binge eating disorder are each associated with PCOS [138].

Eating disorders often cause endocrine abnormalities. Amenorrhea is very commonly found in women with eating disorders, especially anorexia nervosa. Interestingly, though, it was removed as a required diagnostic criterion for the condition in DSM-5 not only because it is irrelevant for men with anorexia nervosa but also because amenorrhea is not found in all patients with the underlying psychological and behavioral features characteristic of the condition. Further, many women are on contraceptives and are without regular menses [139]. In anorexia, starvation leads to decrease in leptin. This leads to reduced secretion of pulsatile GnRH and subsequently decreased LH and follicle-stimulating hormone (FSH) production [140]. This results in anovulation, amenorrhea, and irregular menses. Approximately 50% of women with bulimia nervosa have irregular menses [141]. Bulimia nervosa is associated with low serum levels of LH and FSH, which is thought to cause menstrual irregularity [142]. Binge eating disorder can lead to insulin resistance and increased serum testosterone, which interrupts ovulation and menses [143]. The prevalence of PCOS is 6% in women with bulimia and 18% in those with binge eating disorder [144].

Impact of Psychiatric Disorders on Gynecologic Disease

As we have reviewed, the rates of psychiatric conditions are often higher in patients with several common gynecological conditions, and in a few instances, psychiatric conditions increase the risk of gynecological illness (e.g., anorexia nervosa causing amenorrhea). The relationships between these two classes of conditions are complex. In this section, we focus on the potential impact of psychiatric disorders on gynecologic illness—either as a risk factor for gynecologic disease or a factor that influences the course of gynecologic illness.

Depression

Urinary incontinence may intuitively lead to depression due to functional impairment, but the relationship may, in fact, be bidirectional. For instance, evidence suggests that depression may be a risk factor for urinary incontinence. Three large population-based studies showed that women with baseline depression were more likely to develop urinary incontinence over the study periods [73, 145, 146]. Conversely, in the Norwegian population study, women with baseline urinary incontinence were more likely to develop mild depression during the study period [145]. Similarly, in an 18-year longitudinal study of middle-age women, the onset of depression during the study period was associated with incidence of urinary incontinence [147]. Depression is also associated with the persistence of urinary incontinence [148]. In a study of women with incontinence undergoing midurethral slings, those with depression were more likely to have worse quality of life and sexual functioning before and after surgery [149]. Depression also negatively impacts the outcome of pelvic floor muscle training [150]. Women with more severe depression were less adherent to pelvic floor exercises and had a poor attendance rate; women with depression of moderate severity or greater had poorer outcomes than women with no or mild depression [150].

Despite effective screening methods for precancerous cervical dysplasia and for oncogenic HPV infection, cervical cancer continues to be diagnosed after it has become invasive, and more than half of women with invasive disease at the time of diagnosis have had inadequate or no prior cervical cancer screening [151]. Multiple studies have shown that women with depression do not receive cervical cancer screening consistent with current recommendations [152–155]. However, some care systems may provide more equitable care to those with depression; for instance, a study conducted through the US Veterans Administration found no difference in the rate of cervical cancer screening between those with and without a diagnosis of depression [156]. In a study of Medicaid patients in Maryland that accounted for diagnosis of substance use disorders, women with depression were rather more likely to have cervical cancer screening than women without depression [157].

In women with gynecologic cancer, depression is a risk factor for overall lower quality of life [158], malnutrition [159], and higher readmission rate after surgery [160]. In addition, US women with gynecologic cancer have a 1.4-fold increase in risk of completed suicide compared to the general population [161] and a 30% increased risk of suicide compared to women with non-gynecologic cancers [162]. Among gynecologic cancers, women with ovarian cancer have the highest risk of suicide [161], and this risk is highest in the first year after diagnosis [161–163]. The Surveillance, Epidemiology, and End Results (SEER) program has identified white race, unmarried status, advanced cancer stage, higher grade of cancer, and absence of surgical treatment as risk factors for suicide among women with gynecologic cancer [161]. Depression in women with cancer increases suicide risk [164, 165]; additional risk factors include hopelessness [165], pain, and loss of physical functioning [166].

Bipolar Disorder

The association between bipolar disorder and cancer remains poorly characterized. In a study of the Swedish national registry, bipolar disorder was not found to predict a diagnosis of gynecological cancer [167]. Similarly, a large population cohort study from Taiwan found that female patients with bipolar disorder did not have higher incidence of cancer than those without bipolar disorder [168]. Furthermore, no difference in the incidence of site-specific cancer was found in women in bipolar disorder [168]. Nevertheless, an Israeli population cohort study found that women with bipolar disorder had a 1.75-fold increased risk for all cancers [169].

Anxiety

Anxiety can have a significant impact on health-seeking behaviors in general. In one study, women screened to have anxiety in gynecology clinics had more appointments to the gynecologists and more acute hospitalizations than women who did not screen positive for anxiety [48].

Anxiety may be a risk factor for urinary incontinence as shown in a large prospective population-based study, where baseline anxiety was a risk factor for developing urinary incontinence [145]. Studies have failed to find evidence that anxiety disorders increase the risk of cancer [170]. For women undergoing hysterectomy for benign indications, preoperative anxiety is associated with postoperative pain [171], analgesic use [172], and surgical site infection [173].

Posttraumatic Stress Disorder

Women with PTSD have higher risk for sexually transmitted diseases, urinary tract infections, endometriosis, polycystic ovary syndrome, amenorrhea, chronic pelvic pain, infertility dyspareunia, and cervical dysplasia than women without PTSD [174, 175]. In addition, women who have experienced sexual violence have a higher risk of cervical cancer [176].

Women with sexual trauma and PTSD report distress, fear, pain, and embarrassment during pelvic exams [177, 178]. Although women with sexual trauma have been expected to have a lower rate of cervical screening due to avoidance of pelvic examination, [179, 180], not all women with PTSD have reduced rate of cervical cancer screening. For instance, among the veteran population, there is no evidence that PTSD is associated with decreased cervical cancer screening [156].

An interesting finding is that women with PTSD are at risk for gynecologic morbidities that may require surgery for relief of symptoms. Among female veterans, the prevalence of hysterectomy was higher than the civilian population [181, 182]. The mean age of hysterectomies in the veteran population is much younger than the general population [182]. Furthermore, veterans with PTSD are at higher risk for hysterectomy than those without PTSD [182].

Schizophrenia

Menstrual irregularities are common in women with schizophrenia. Antipsychotic medications can increase serum prolactin level, which can subsequently cause galactorrhea [183]. Hyperprolactinemia indirectly inhibits pulsatile secretion of LH manifesting as anovulation and amenorrhea [183]. Despite this direct effect of antipsychotic medications on ovulation, the impact of schizophrenia and its treatment on infertility is not well established. In Denmark, where fertility treatment is provided by the national healthcare system, the prevalence of psychotic disorders was 0.6% of women seeking assisted reproductive technology (ART) [184]. Of these women with psychotic disorders and seeking ART, 42% of the psychotic disorders were acute or transient in nature, 17% schizophrenia, and 3% schizoaffective disorder [184]. ART treatment was less successful in women with psychotic disorders than in women without psychotic illness [184].

Data on a potential association between cancer and schizophrenia are inconsistent. Based on a Swedish cohort study, people with schizophrenia and their first-degree relatives were found to have lower risk of cancer [185]; however, a similar study among Asian women found that schizophrenia was associated with a 1.31-fold increased risk of all cancers [168]. Women <50 years of age had a 1.61-fold increased risk for cervical cancer and a 2.71-fold increased risk of uterine cancer [168]. Finally, a population-based cohort study of people with mental illness was unable to find that women with schizophrenia were at increased risk for all cancers, but these women with schizophrenia did have overall greater mortality [186]. Women with schizophrenia have been shown to be less likely to present for cervical cancer screening [187, 188]. In fact, women with schizophrenia are less likely to have cervical cancer screening than women with depression or bipolar disorder [189, 190]. A study from the UK showed that history of schizophrenia, the use of long-acting injectable antipsychotic medication, a higher severe mental illness severity (as defined as having a psychiatric hospitalization, treatment under the Mental Health Act, difficulty managing their physical health or contact with Assertive Outreach, Crisis team or Accident and Emergency liaison team), and a higher severe mental illness risk (as defined as history of violent or offending behavior using data from a risk assessment violence and aggression subscale) are risk factors for nonadherence with cervical cancer screening [191].

Schizophrenia or its treatment can cause or influence urinary incontinence by a few mechanisms. First, antipsychotic medications have been associated with urinary incontinence. Next, polydipsia is a common finding in patients with schizophrenia, perhaps leading to polyuria and subsequent urinary incontinence. Further, schizophrenia has been associated with detrusor hyperreflexia [192]. In a national survey of US female nursing home residents, 38% of women with schizophrenia were found to have urinary incontinence [193]. In a large cross-sectional population-based study, patients with schizophrenia had a 1.78-fold higher risk of developing urinary incontinence [194]; however, when women and men were analyzed separately, female patients with schizophrenia were not independently at higher risk of urinary incontinence. This sex difference in the association between schizophrenia and urinary incontinence may be explained by the fact that women are more likely to have stress incontinence which is related to laxity in pelvic structures, whereas men are more likely to have urge incontinence [195] which is related to detrusor hyperreflexia.

Substance Use Disorders

Alcohol may be associated with lower risk of urinary tract symptoms and less urinary incontinence. In a US study, women who have more than one standard drink a day had a higher risk of voiding symptoms such as incomplete bladder emptying, intermittency, weak urinary stream, and hesitancy [196]; however, two large European studies failed to show an association between alcohol intake and urinary incontinence [197, 198]. For women who already have urinary incontinence, alcohol use is associated with persistence of urinary incontinence [196].

Alcohol use has been associated with infertility, especially in women [199, 200]. Alcohol consumption has been associated with fewer oocytes, poorer quality embryo, and lower pregnancy rates in women undergoing ART treatment [201, 202]. A meta-analysis concluded that women who drink alcohol have a 1.24-fold increased risk for endometriosis compared to abstainers [203].

Alcohol can increase risk of colorectal, breast, liver, oropharyngeal, and laryngeal cancers, but its effect on gynecologic cancer remains inconclusive [204]. The association between endometrial cancer and alcohol use has been of particular interest to researchers because alcohol is known to increase estrogen levels. Endometrial cancer is associated with excess estrogen with low progesterone serum levels as well as hyperinsulinemia and insulin resistance [205]. However, the relationship may be more complex. Lower levels of alcohol use may even have a protective effect because moderate alcohol consumption improves insulin sensitivity [206]. Prospective population trials have not found alcohol consumption to be associated with increased risk of endometrial cancer [207–216], but the risk of endometrial cancer may still be related to the amount of alcohol use. A large prospective study in the USA showed that women consuming two or more drinks a day had a twofold increased risk for endometrial cancer compared to nondrinkers but there was no increased risk of endometrial cancer in women who consumed less than two drinks a day [217]. A meta-analysis of prospective cohort trials suggests that <1 drink per day decreases the risk of endometrial and >2 drinks per day increases the risk, but these results failed to reach statistical significance [209]. A more recent meta-analysis including three newer prospective cohort trials similarly failed to find an association between alcohol and endometrial cancer risk [218].

Risk factors for ovarian cancer include family history, nulliparity, early menarche, and late menopause, and protective factors include pregnancy, breastfeeding, oral contraceptive use, and tubal ligation [219]. The fact that alcohol increases serum estrogen provides a basis for how it could theoretically increase the risk of ovarian cancer, but studies investigating a potential association remain inconclusive. For instance, certain cohort studies have reported increased risk of ovarian with alcohol [212, 220], whereas others reported decreased risk [221]. Two recent meta-analyses were unable to identify an association between alcohol and ovarian cancer [222, 223].

Chronic alcohol use is associated with increased surgical complications and may, therefore, impact gynecological disease that requires surgical intervention. About one in ten women having a hysterectomy has alcohol use disorder [224]. Importantly, even hazardous drinking, which is defined as >3 drinks a day, has been associated with operative complications such as bleeding episodes, postoperative infection, and cardiopulmonary complications [225]. For women undergoing hysterectomy, women who consumed >60 mg of alcohol a day had a higher complication rate than women abstainers or those consuming ≤60 mg daily [224]. Patients may not voluntarily disclose alcohol use to their surgeons. Further, patients may not be aware of the risk of alcohol withdrawal with abrupt cessation or the risk that alcohol use poses for potential surgical complications.

Eating Disorders

A retrospective linkage study examining women with anorexia nervosa and cancer found no increase in the incidence in overall or gynecologic cancer [226]. However, there is a 2.7-fold increased risk of mortality in women with anorexia nervosa who are diagnosed gynecologic cancer [226]. The reason for this increased risk of mortality may be related to delay in cancer diagnosis, poor medical health, and therefore less aggressive treatment [138]. Bulimia nervosa and binge eating disorder have each been associated with PCOS, and PCOS has been independently associated with endometrial cancer. However, there is no clear link between either bulimia nervosa or binge eating disorder and endometrial cancer.

Treatment of Psychiatric Disorders in Gynecologic Patients

Major Depressive Disorder

Antidepressants, psychotherapy, and their combination are the mainstays of depression treatment. Community samples suggest that patients prefer psychotherapy to medications in a 3-to-1 ratio [227]. Cognitive behavioral therapy (CBT) is an evidence-based, structured, time-limited, collaborative therapy that modifies distorted thinking and maladaptive behaviors. Women with severe depression should be offered an antidepressant based on treatment guidelines published by the American Psychiatric Association. Given their safety profile, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are widely considered first-line treatment. Other common antidepressants include bupropion and mirtazapine. Up to 50% of gynecologists consider themselves as primary care providers [228]; however, time constraints and perceptions of inadequate training are barriers to treating depression [229]. Therefore, a collaborative model in an obstetrics and gynecology office can provide a more comprehensive means of screening and treating depression [230, 231].

Even though depression and depressive symptoms are common in women with gynecologic cancer, randomized controlled trials in the cancer population are limited. Psychosocial interventions are often a part of a comprehensive cancer program. Patient education alone has not been found to improve depression or quality of life [232]. CBT for depression has been found to be as efficacious as medications in one meta-analysis [232]. Psychosocial interventions before cancer surgery, known as prehabilitation, have also been studied in various cancers, but more studies are needed to know whether they prevent or treat depression [37].

In experimental models, SSRIs and tricyclic antidepressants have been associated with cancer growth [233]. However, clinically, the association between antidepressants and gynecologic cancer is inconsistent [234, 235]. Large population-based studies have not found an association between antidepressant use and ovarian, endometrial, or cervical cancer [236–238]. Likewise, a multicenter trial revealed no association between SSRI use and overall mortality of women with ovarian cancer, but SSRI use was associated with decreased time to recurrence of disease [239]. It is important to keep in mind that population-based associations such as these are at high risk of confounding bias since they typically do not control for all variables relevant for models of cancer risk or clinical outcome.

In clinical practice, selection of an antidepressant for oncology patients with depression may depend on the side effect profile. The histamine receptor agonist and 5HT2 and 5HT3 receptor antagonists of mirtazapine can promote sleep and appetite and act as an antiemetic. Bupropion is a norepinephrine and dopamine reuptake inhibitor that can be activating for an oncology patient with fatigue. However, at daily doses of 400 mg or more, bupropion can lower the seizure threshold, and it should be used in caution in patients with decreased oral intake and electrolyte abnormalities, history of seizure disorder, or an intracranial mass. Psychostimulants such as amphetamine and modafinil are also used in oncology patients with fatigue.

Bipolar Disorder

Lithium is approved drug by the US Food and Drug Administration (FDA) for the treatment of mania and maintenance of bipolar disorder. Lamotrigine is FDA-approved for maintenance of bipolar disorder. Other antiepileptic medications such as valproic acid and carbamazepine are also commonly used to treat of bipolar disorder, but they are approved by the FDA specifically for bipolar mania. In addition, the second-generation antipsychotics aripiprazole, ziprasidone, quetiapine, olanzapine, and risperidone can be used to treat mania [240]. Quetiapine, lurasidone, and the combination pill containing olanzapine and fluoxetine are FDA-approved for bipolar depression. Electroconvulsive treatment (ECT) can also be used during acute mania or bipolar depression, and ECT remains an option during pregnancy [241–243].

Treatment of bipolar disorder in reproductive age women requires special considerations. Lithium, valproic acid, and carbamazepine are teratogenic, and women of reproductive age must be counseled accordingly. Many women with bipolar disorder who do not wish to become pregnant will use oral contraceptive while on these agents; however, caution must also be taken given drug-to-drug interaction. Carbamazepine induces cytochrome P450 3A4 and can potentially decrease the efficacy of oral contraceptives [244]. Combined oral contraceptive reduces the serum concentration of lamotrigine and valproic acid by induction of glucuronosyltransferase by ethinyl estradiol [245, 246].

Premenstrual Dysphoric Disorder

SSRIs are the first-line treatments for premenstrual dysphoric disorder (PMDD) [247]. Fluoxetine, paroxetine, and sertraline are FDA-approved for PMDD. Unlike in treatment of depression, SSRIs have shown clinical benefits within days to 4 weeks of initiation with reduction of psychological symptoms of PMDD during first menstrual cycle of treatment [248]. Both continuous and luteal phase only use of SSRI are efficacious for treating PMDD [249]. Other interventions include oral contraceptives, especially those with drospirenone, CBT, and gonadotrophin hormone analogs which are also treatment options for PMDD [247].

Anxiety Disorders

Generalized anxiety disorder and panic disorder are commonly encountered by gynecologists. Women with moderate symptoms of generalized anxiety disorder or panic disorder can be offered medication or psychotherapy such as CBT. If CBT is not available or unpreferable to the patient, an antidepressant (typically an SSRI) is recommended as a first-line pharmacologic intervention [250]. SNRIs may also be considered, but withdrawal symptoms tend to be more severe with SNRIs and may notably include paresthesias [250]. Benzodiazepines should be prescribed only for short-term use while an antidepressant is being titrated [251, 223]. Buspirone is also a reasonable choice for generalized anxiety disorder [252].

Presurgical anxiety is common, and 75% of anesthesiologists report prescribing their patients benzodiazepines before surgery [253]. Although clinically effective for pre-procedural anxiety, preoperative use of benzodiazepines is not expected to have postsurgical benefit. For instance, in a randomized trial of women undergoing hysterectomy, diazepam (10 mg) use prior to surgery did not decrease postsurgical morphine use [254]. Interestingly, though, melatonin (5 mg) [255] and clonidine (100 μg) [256] administered preoperatively have been shown to be associated with decreased post-hysterectomy analgesic use, but a similar benefit was not found with preoperative gabapentin (600 mg) [257]. A small pilot study using Reiki therapy prior to hysterectomy found shorter operative time and lower anxiety at time of discharge [258].

Posttraumatic Stress Disorder

Cognitive processing therapy, prolonged exposure, and eye movement desensitization and reprocessing are evidence-based treatments of PTSD [259]. These trauma-focused psychotherapies have been found to be more efficacious than medications [260]. The National Center of PTSD overseen by the US Veterans Administration recommends trauma-focused psychotherapies as first-line treatment and considers medications and non-trauma-focused psychotherapies as alternatives only if trauma-focused psychotherapy is unavailable, ineffective, or declined by a patient [261]. If pharmacotherapy is selected, sertraline, paroxetine, fluoxetine, and venlafaxine are considered superior to other antidepressants in treating PTSD [259, 260]. Both trauma-focused psychotherapy and pharmacotherapy showed efficacy even when women were analyzed separately than men [259].

Schizophrenia

Schizophrenia typically requires comprehensive treatment planning that includes medication management as well as case management, vocational support, and housing and supportive services. Given the theorized neuroprotective effects of estrogen, the use of estrogen replacement therapy and selective estrogen-receptor modulators as an adjunct to antipsychotics during menopause has been found to improve negative symptoms, reduce extrapyramidal symptoms, and prevent tardive dyskinesia. In a small cross-sectional study of postmenopausal women with schizophrenia on antipsychotic medications, those who received estrogen replacement therapy had less severe negative symptoms [262]. Estrogen has also been used as an adjunct in premenopausal women with schizophrenia with positive results [263, 264]. Similarly, selective estrogen-receptor modulators such as raloxifene as an adjunct to antipsychotic medications may improve symptoms of schizophrenia in postmenopausal women [265]. Raloxifene may also be efficacious as an adjunctive agent in women with refractory schizophrenia [266]. Higher serum estrogen has also been associated with decreased extrapyramidal symptoms in women on antipsychotic medications [267]. Although these results are promising, most of the studies on the use of estrogen in women with schizophrenia have small sample sizes but deserve further investigation. Given the preliminary nature of these results, estrogen should be prescribed only for gynecologic indication, not to treat psychotic illness.

Substance Use Disorders

Treatment of substance use disorders ideally encompasses a combination of medications, behavioral intervention, psychosocial support, and medical care [268]. Although underutilized, medication management for alcohol use disorder is associated with fewer inpatient admissions and lower healthcare costs [269]. Disulfiram, considered an aversive therapy, is the oldest medication available for alcohol use disorder and acts by inhibiting aldehyde dehydrogenase [270]. When a patient on disulfiram drinks alcohol, alcohol is metabolized to aldehyde, which then accumulates leading to an unpleasant syndrome of nausea, vomiting, and facial flushing [271]. Naltrexone is a mu-opioid antagonist FDA-approved for alcohol and opioid dependence. By blocking activation of endogenous opioids released by alcohol ingestion, it decreases dopamine release in the reward pathway [272]. A systematic review showed that women who used naltrexone had decreased amount of alcohol consumption and longer time to relapse compared to those on placebo [273]. Naltrexone is also available in a monthly intramuscular injection. In the perioperative setting, it is important to remember that the patient should not be opioid-free for 7–10 days before starting naltrexone, in order to avoid withdrawal which naltrexone can precipitate. Acamprosate is similar in structure to amino acids such as glutamate [274]. Its mechanism of action remains speculative, but it is thought to combat the hyper-glutamatergic state in chronic alcohol use [274]. Unlike naltrexone, acamprosate is excreted exclusively by the kidney and is not metabolized by the liver. A meta-analysis of acamprosate in women found acamprosate was superior to placebo in the percent of abstinent days, rate of abstinence, percent of no heavy drinking days, and rate of no heavy drinking [275].

Chronic alcohol use has been associated with surgical complications and postsurgical withdrawal. A meta-analysis of randomized controlled trials found that patients who received disulfiram preoperatively to achieve abstinence had lower complication rates [276]. Studies have shown that abstinence from alcohol for 3–8 weeks often reverses the effects of alcohol on postoperative bleeding time, arrhythmias, and delayed-type hypersensitivity reactions in patients undergoing surgery [277].

Methadone, buprenorphine, and naltrexone are the three FDA-approved medications for opioid use disorder. Methadone is a full mu-opioid agonist that is dispensed only from a licensed opioid treatment program. Buprenorphine is a partial mu-opioid agonist that can be prescribed only by a physician with special certification (a so-called X-license). When prescribed for pain, buprenorphine is given as an individual agent, but when prescribed for opioid use disorder, buprenorphine is formulated with naloxone, an opioid antagonist. Sublingual administration of buprenorphine/naloxone allows for absorption of buprenorphine alone; naloxone is not absorbed trans-mucosally or enterally. However, naloxone is included to deter diversion or abuse because it counteracts opioid activity when injected causing immediate opioid withdrawal. Naltrexone, a mu-opioid antagonist, is approved for relapse prevention by blocking opioid receptors; as mentioned above, naltrexone is available as a daily oral medication or monthly injection.

Eating Disorders

Treatment of eating disorders, especially anorexia nervosa, will require a medical team including nutritionists and mental health professionals. Patients with anorexia nervosa may require nutritional and medical stabilization requiring hospitalization due to the potential for refeeding syndrome and cardiac arrhythmias. There is currently no FDA-approved medication for the treatment of anorexia nervosa; however, psychiatric comorbidities such as depression and anxiety deserve pharmacological management. Bupropion can lower the seizure threshold and should be avoided in patients with eating disorders [278]. Atypical antipsychotics such as olanzapine and quetiapine have been used in small open-labeled trials to enhance appetite and improve body mass index, and they may have modest effects on obsessional symptoms about food, weight, and body image [279–282]. However, the side effects of atypical antipsychotics such as risk of prolonged QTc, reduced insulin sensitivity, extrapyramidal symptoms, and tardive dyskinesia should be monitored closely. Medications to induce menses artificially are not recommended [283]. Psychotherapy, including family therapy especially in adolescents, is recommended for patients with anorexia nervosa once they are stabilized medically [284, 285].

Fluoxetine at 60 mg/day is approved by the FDA for treatment of bulimia nervosa. At this dose, there is an improvement in binging and purging behaviors [286]. As stated above, bupropion can lower seizure threshold and therefore contraindicated in women with bulimia nervosa. Topiramate has also been found to improve binging, purging behaviors, and weight loss [287, 288].

Lisdexamfetamine is approved by the FDA for treatment of binge eating disorder. It reduces obsessions and compulsions related to binge eating [289] and reduces the number of binge-eating days and risk of relapse [290]. Topiramate alone or with CBT has been shown to reduce binge eating and weight [291, 292].

Nonpsychiatric Use of Psychotropics

Menopausal-Related Vasomotor Symptoms

Vasomotor symptoms (VMS) occur in three-quarters of menopausal women. For many women, especially those with hormone-sensitive cancers, hormone replacement therapy is not an option to ameliorate VMS. Based on evidence, the North American Menopause Society recommends cognitive behavioral therapy and, to a lesser extent, clinical hypnosis as non-pharmacological treatments of VMS [293]. Paroxetine is the only non-hormonal medication to have been FDA-approved for treatment of VMS, but selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) including escitalopram, citalopram, venlafaxine, and desvenlafaxine have been shown to be effective in treating VMS in randomized, double-blind, placebo-controlled trials [293]. Gabapentinoids such as gabapentin [294, 295] and pregabalin [296] have also been shown to be effective in treating VMS. Clonidine, an alpha 2 adrenergic agonist, has been shown to be more effective than placebo for VMS, but less effective than SSRIs, SNRIs, and gabapentin [293].

Chronic Pelvic Pain

Tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors have been used to treat pain in various conditions. Tricyclic antidepressants have limited data in chronic pelvic pain (CPP), and side effects from anticholinergic properties also can make this class of medication difficult to tolerate. Duloxetine is FDA-approved for fibromyalgia, musculoskeletal pain, and osteoarthritis, and venlafaxine is FDA-approved for pain syndrome. However, evidence for SNRIs in chronic pelvic pain is inconclusive [297]. Current data using gabapentin and pregabalin on CPP is limited, but a small pilot randomized trial using gabapentin shows some promise at 6 months use when compared to placebo [298].

Conclusion

Unlike other surgical specialties, gynecologists have a longitudinal relationship with their patients. More than just surgeons, they are considered women's healthcare physicians. Psychiatric symptoms and disorders are common and may impact adversely either directly or indirectly on gynecologic conditions. While reproductive psychiatry has emerged as a psychiatric subspecialty focused on psychiatric disorders during pregnancy and the postpartum period, psychiatric conditions or symptoms associated with gynecologic conditions are less well characterized and studied. At this time, treatment of psychiatric disorders in women is not unlike that for men except for attention to teratogenicity. In the future, as empiric studies on gender differences continue to emerge, psychiatric care in gynecologic patients will be better informed.

Take-Home Points

- Hysterectomy is one of the most common gynecologic surgeries. When the hysterectomy is performed for a benign indication, improved quality of life including sexual function and pain and reduction in psychiatric symptoms is common.
- Postoperative delirium is common after gynecologic surgery especially in the elderly population who are more likely to undergo surgery for gynecologic cancers and pelvic floor dysfunction. At this time, prevention and treatment of delirium gynecologic patients are similar to those in the general postoperative population.
- Women are more likely than men to have depressive disorders and anxiety. Gynecologists can play a pivotal role by screening for these conditions in their patients.
- Women with leiomyomata, endometriosis, polycystic ovarian disease, urinary incontinence, pelvic organ prolapse, and gynecologic cancer have been associated with depression. Depressive symptoms tend to improve after surgery to relieve symptoms and treatment of these conditions.
- Treatment of depression in gynecologic patient is similar to that of the general population with medications such as SSRIs and SNRIs as the first-line therapy. Evidence-based therapy such as cognitive behavioral therapy (CBT) can be used as an alternative to

or adjunctively with medications. SSRI is also the first-line treatment for premenstrual dysphoric disorders.
- Women of reproductive age with bipolar disorder should be counseled regarding potential teratogenic effects of lithium, valproic acid, and carbamazepine.
- Anxiety disorders can be treated with antidepressants and CBT. Long-term use of benzodiazepine is not recommended. Preoperative use of benzodiazepine may be helpful for anxiety before a procedure; however, there is no postoperative benefit.
- Treatment of gynecologic patients with schizophrenia, substance use disorders, and eating disorders will require a multidisciplinary approach.
- Psychotropics can be used for gynecologic conditions such as vasomotor symptoms and chronic pelvic pain. While paroxetine is the only antidepressant that is FDA-approved for vasomotor symptoms, other SSRIs and SNRIs have also been in clinical studies. Tricyclic antidepressants and SNRIs have been used in treating chronic pelvic pain; however, the evidence is inconclusive.

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15 Perioperative Psychiatric Conditions and Their Treatment in Children and Adolescents

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Introduction

As of 2014, there are approximately 74.2 million children under 18 years of age in the USA, accounting for 23.1% of the total US population. It is estimated that pediatric surgeons perform four million procedures in the USA annually [1]. In 2009 alone, they performed 200,000 inpatient pediatric procedures, and of these 40% were performed in an adult hospital. The type of surgical procedure performed can range from elective to emergent. In fact, both the surgery itself and the illness for which surgery is indicated can engender a great deal of distress in pediatric patients and their caregivers, which calls for a developmentally informed approach during the perioperative period. Given the volume of surgical procedures performed each year, such an approach could have a far-ranging, beneficial influence on this vulnerable pediatric population.

In light of the above, this chapter will begin with a discussion of the most common surgical procedures performed in children. It will then present the children's conception of illness to set the stage for a developmentally informed approach to the more common perioperative psychiatric conditions seen in this population, namely, anxiety, depression, aggression/agitation, and delirium. These aforementioned conditions will be examined in depth in the subsequent section. The chapter will conclude with a discussion of management of these conditions.

Overview of the Most Common Surgeries in Children

The evolution of pediatric surgery closely follows that of adults, as the advances achieved in adult surgery are often later adopted in surgery for children. In the second century, only the science of anatomy was available to the surgeon; the main subjects of study were simply muscles, nerves, and blood vessels. Based on this limited knowledge, surgical techniques were rudimentary and success rates low. Therefore, infants and

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children born with defects such as skeletal deformities, cleft lip, and imperforate anus often did not survive surgical attempts [2].

It was not until the fifteenth century when Leonardo da Vinci provided some of the first detailed anatomical drawings of humans that the science of surgery truly began to expand. In the sixteenth century, esophageal atresia and other malformations were described as a result of autopsy, but surgical interventions for these defects did not exist at the time [3]. This changed in the seventeenth and eighteenth centuries in Basel, Switzerland, when Johannes Fatio began to develop surgical interventions for these long-tolerated conditions [4, 5].The first colostomy for a baby with imperforate anus was performed in 1793, and since that time surgery has continued to make advances [6].

The focus of this chapter is on perioperative psychiatric conditions and their management in children and adolescents. We will begin by first reviewing the most common surgeries performed in children.

Congenital Heart Disease

Congenital heart diseases are the most common congenital defects in children, with an incidence of 0.5–1% of live births [7]. They can be divided into acyanotic and cyanotic diseases.

Acyanotic diseases include *ventricular septal defect* (VSD), the most common congenital defect, accounting for 25% of all congenital heart disease. Small VSDs close spontaneously; if not, surgical closure may be required. Large VSDs are often symptomatic and usually require surgical correction [8]. *Atrial septal defect* (ASD) is the next common acyanotic disease accounting 10% of all congenital heart defects. ASDs usually close spontaneously by age 3. If surgery is indicated, an ASD closure device can be inserted via cardiac catheterization [8]. *Patent ductus arteriosus* (PDA) represents approximately 5–10% of all congenital heart disease conditions. PDA normally closes within 12–24 h after delivery. If not, surgical management involves occlusion of the PDA by surgical clip, silk ligature, or by division between ligatures. This surgery is normally performed in the neonatal intensive care unit [8]. *Endocardial cushion defect* is also referred to as atrioventricular canal defect and may be complete or partial. It is most commonly seen in children with Down syndrome. The treatment is surgical correction [8]. *Pulmonary stenosis* and aortic stenosis occur in approximately 10% and 5% of congenital heart defects in children. The treatment is balloon valvuloplasty for both; if this fails, surgical repair is necessary [8]. *Coarctation of the aorta* accounts for 10% of congenital heart defects, and it is almost always associated with structural abnormalities such as hypoplastic aortic arches, abnormal aortic valves, and VSDs. Management involves administration of prostaglandin E1 to keep the PDA patent until balloon angioplasty can be performed [8].

Cyanotic diseases commonly refer to the "five T's": tetralogy of Fallot, transposition of the great arteries, tricuspid atresia, truncus arteriosus, and total anomalous pulmonary venous return. Infants with such defects will present with cyanosis, respiratory distress, and hypoperfusion. *Tetralogy of Fallot* is the most common cyanotic heart defect, comprising 10% of all congenital heart defects. There are four structural defects: VSD, pulmonary stenosis, overriding aorta, and right ventricular hypertrophy. Management involves complete surgical correction with VSD closure and removal of pulmonary stenosis. *Transposition of great arteries* comprises 5% of congenital heart defects. It is the most common cyanotic heart defect of the newborn period. Initial treatment with prostaglandin E1 is required to maintain the PDA, then balloon atrial septostomy, and ultimately complete surgical repair with arterial switch is performed. *Tricuspid atresia* represents 2% of congenital heart defects. Management involves administration of prostaglandin E1 to maintain flow followed by surgery. *Truncus arteriosus* and *total anomalous pulmonary venous return* each account for less than 1% of congenital heart defects and require surgical repair. Less commonly occurring than the five T's is *hypoplastic heart*, which represents 1% of congenital heart defects. It is the most common cause of death from a cardiac defect in the first month of life [9].

Gastrointestinal Surgery

Among congenital GI conditions, *cleft lip* is the most common orofacial malformation with incidence of 1 in 700 live births [10]. In the USA, cleft palate affects 0.3–0.5 per 1000 live births [11]. Management is surgical correction at 3–6 months of age depending on the severity of the malformation. *Congenital anomalies of the esophagus* predominantly include tracheoesophageal fistula with esophageal atresia, in which the esophagus ends in a blind pouch, with a fistulous communication between the esophagus and trachea. The most common type is distal tracheoesophageal fistula associated with esophageal atresia. Management involves surgery to repair fistula, followed by direct esophageal anastomosis [12]. *Anorectal malformations* occur in 1 in 5000 live births. The most common defect in females is a rectovestibular fistula, whereas the most common defect in males is a rectourethral fistula. Imperforate anus without fistula occurs in 5% of patients; patients with Down syndrome and anorectal malformations have imperforate anus 95% of the time. Management for each of these is posterior sagittal anorectoplasty [13].

For acquired GI conditions, *appendicitis* remains the most common acute surgical condition of the abdomen in children [14], affecting 1 in every 1000 children a year in the USA [15]. Management is surgical removal of the appendix. *Hypertrophic pyloric stenosis* is the most common cause of gastric outlet obstruction in an infant, occurring at a rate of 1.5–4.0 per 1000 live births. Management involves splitting the hypertrophied pyloric muscle to the submucosa and closing the muscle transversely [16].

Inflammatory bowel disease (IBD) principally includes ulcerative colitis (UC) and Crohn's disease (CD) and affects 7/100,000 children per year in the USA and has a prevalence of up to 20/100,000 [17]. Due to the indolent course of IBD, it often negatively affects growth and development of children [18, 19]. Surgical management can involve several different colorectal procedures including, for instance, proctocolectomy with ileal pouch-anal anastomosis (IPAA) [20]. *Necrotizing enterocolitis* is an acquired inflammatory gastrointestinal disease that exclusively affects the newborn gut and has an incidence of 1–3 per 1000 live births. It is the most common newborn surgical emergency, and, among neonatal GI conditions requiring surgical intervention, it is the leading cause of infant morbidity and mortality. Management includes complete bowel rest with bowel decompression. In severe cases, such as with bowel perforation, exploratory laparotomy for resection, enterostomy, and mucous fistula is necessary [21].

Hirschsprung disease is a disorder characterized by absence of myenteric and submucosal plexuses of the distal intestines, leading to lack of peristalsis and functional intestinal obstruction due to absent ganglions. Its incidence is 1 in 5000 live-born infants. Surgical management involves rectosigmoidectomy with preservation of the sphincters and subsequent colostomy [22].

Surgeries of the Central Nervous System (CNS)

Brain tumors, or neoplasms, are a leading cause of death in children less than 19 years of age, second only to head trauma. Tumors of the CNS are the most common solid neoplasm found in the pediatric population, and they account for 20% of cancer deaths, which is second only to leukemia [23, 24]. An estimated 4830 new cases of childhood primary malignant and nonmalignant brain and other CNS tumors are expected in the USA in 2017 [25]. Signs and symptoms of brain tumors often involve headache, nausea, vomiting, lethargy, change in personality, and worsening school performance [26]. The location of the brain tumor and patient age are the most important factors in diagnosing brain tumors in children.

Pediatric tumors are often divided into those occurring above (supratentorial) or below (infratentorial) the tentorium. Supratentorial tumors involve the cerebral hemispheres, basal ganglia, and thalamus; infratentorial tumors involve the pineal gland, tectum, pons, medulla, and cerebellum [26]. In children younger than 2 years of age, brain tumors tend to be supratentorial. From the ages of 3–5, they tend to be infratentorial [23]. Prognosis is very poor in children younger than 1 year of age with the exception of choroid plexus papilloma [23]. Surgical intervention involves tumor debulking, with the goal of debulking as much tumor as possible to obtain a histological diagnosis and to reestablish normal cerebrospinal fluid pathways. Radiation and/or chemotherapy may follow. Surgical complications may include acute hydrocephalus, aseptic meningitis, pseudomeningoceles, mutism, pseudobulbar palsy, cranial nerve or brainstem dysfunction, and gastrointestinal hemorrhage [27, 28]. Patients may develop swallowing dysfunction, predisposing them to aspiration pneumonia that requires both a tracheostomy and feeding tube [26].

Transplantation Surgery

In the last 50 years, significant progress has been made in the replacement of failing organs with healthy solid organs, tissues, and cells [29]. The most common transplantation surgeries in children include kidney, liver, heart, and lung transplant.

Kidney transplantation is the treatment of choice for children with end-stage renal disease [30]. The most common pathologies necessitating kidney transplant in the pediatric population include renal aplasia, hypoplasia, dysplasia, obstructive uropathy, focal segmental glomerulosclerosis, reflux nephropathy, and chronic glomerulonephritis.

In young children, congenital causes are more prevalent. In older children, acquired disease is more common. As a rule, children with end-stage renal disease should be considered for transplantation. Rare absolute contraindications include malignancy or systemic sepsis [31].

Liver transplantation is the treatment of choice for a variety of conditions. These include decompensated cirrhosis, malignancies of the liver and biliary tract such as hepatoblastoma and hepatocellular carcinoma (these can be due to hepatitis C, tyrosinemia, and some glycogen storage diseases), acute liver failure, and many metabolic derangements such as Wilson disease, ornithine transcarbamylase deficiency, and Crigler-Najjar disease [32]. In 2015, a total of 7127 liver transplants were performed in the USA, and of these 580 were pediatric [33]. The most common indication for liver transplant is cholestatic liver diseases, with biliary atresia being the most common of this disease type [32]. Inborn errors of metabolism are a novel but not uncommon indication for transplantation in children, constituting 9% of liver transplants in children [32]. While nearly 65% of pediatric liver transplant recipients are less than 6 years of age, only 25% of their respective cadaveric donors are from the same age group [34]. Survival rate is 90% at 1 year and 80% at 5 years, with many children not only surviving into adolescence and adulthood but also enjoying a good quality of life [35].

Heart transplantation has been performed since the mid-1980s and with the introduction of immunosuppressant agents has become lifesaving for many infants and children. Approximately 400 heart transplants are performed annually in the USA in patients younger under 18 [34]. Due to scarce organ availability, one in four infants will die while awaiting a suitable heart donation [36, 37].Heart transplantation is the treatment of choice for infants with congenital heart disease that cannot be treated with any other modalities; cardiomyopathy is the most common indication for heart transplantation in infants and children [38].

From the late 1990s, *pediatric lung transplantation* has become a viable treatment option for children with end-stage pulmonary disease [39]. However, the number of children undergoing transplantations throughout the world since 1989 is small, representing only 4% of all lung transplantations performed [39]. The most common indications for lung transplantation are cystic fibrosis, interstitial lung disease with pulmonary fibrosis, primary pulmonary hypertension (also associated with congenital heart disease), and retransplantation [39].

Other Surgeries

An inguinal hernia is an abnormal protrusion of abdominal contents through the inguinal canal. Inguinal hernia repair remains the most common operation performed by pediatric surgeons. The incidence in children ranges from 0.8% to 4.4% [40, 41]. Surgical repair involves tightening of the external ring and reconstruction of the posterior inguinal floor [41].

The Concept of Illness in Children

According to Harris et al., "the impact of surgery on stress, anxiety, and ability to cope varies based on the age and developmental stage" of the child [42]. Also important to consider is how the child's stage of cognitive development influences their ability to understand the concept of illness and adapt to illness and surgery [43]. A child's ability to understand illness advances with age provided that growth and development are not stunted, for instance, due to the illness itself, nutritional deficiencies, or psychological privation [43–45]. As children develop, their cognitive sophistication develops as well, and they are less likely to have misconceptions about illnesses and procedures [43, 46]. Building on the earlier works of Piaget and Werner on cognitive development in children, Bibace and Walsh introduced a now widely accepted model of children's concepts of illness, which attempts to explain how a child's understanding of illness develops during their early years [43, 45, 47, 48].

Ages 0–2 Years

During this prelogical stage, the child learns by using their five senses and movements [43, 49]. Children younger than 2 typically express their emotions nonverbally [49]. They depend on the caregiver for their psychological and physical needs [50]. At this age, separation from the primary caregiver is the principle stressor prior to a surgical procedure. Infants and toddlers may also develop anxiety from unfamiliar faces and white coats [50].

Ages 2–7 Years

During this pre-operational stage, children engage in fantasy and magical thinking. They are egocentric in their worldview. They do not have logical or abstract thoughts but are able to understand simplistic concepts such as cause and effect [49].

They are verbally fluent, but they misunderstand words that require abstract thought. For instance, the medical terms "flushing" the IV or pulmonary "toilet" may conjure mental images of a porcelain toilet.

Building on the theories proposed by Bibace and Walsh, Marin describes four strategies children use to explain illness: phenomenism, contagion, immanent justice, and magical thinking [43]. *Phenomenism* is an attempt to explain illness by attributing it to unrelated phenomena (e.g., "I am sick because there was an earthquake near where I live"). *Contagion* is an attempt to explain illness due to being near objects without physical contact (e.g., "I am sick because my dead grandma's couch was brought into the house"). *Immanent justice* explains illness as due to misdeeds (e.g., "I am sick because I yelled at my dad"). *Magical thinking* involves the use of magic as an explanation for the illness. This arises out of the child's inability to think abstractly (e.g., "I got sick because I wished I could play outside longer") [42].

In this age group, children are familiar with parts of their body they can sense. For example, children are aware of the heart because it beats and of their bones because they are harder than skin. However, they do not understand insensate bodily functions or subtler physiological phenomena, such as the flow of blood throughout the body. This concrete way of thinking may lead children to believe that a surgery simply involves taking a nap or a visit to a doctor means getting painful shots [45].

Ages 7–11 Years

During the concrete operational stage, the child acquires the capacity for rational thought, abstract thinking, and hypothetical and deductive reasoning. They are also less egocentric in their worldview. At this age, children may still harbor misconceptions about surgery, fear of pain, and fear of separation from their parents [50]. Many children continue to believe that surgery is a punishment for misconduct. This worldview should be discussed openly with the child because they tend not to disclose this view readily [50]. In this age group, causality of medical illness or surgery is usually explained by internalization or contamination. *Internalization* is an attempt to explain illness by means of having ingested or inhaled something (e.g., "I am sick with the cold because I breathed in cold air") [51]. Children early in this stage, though, still have a limited understanding of their internal organs and how they function. As a result they may still have trouble with the concept of how inhaling germs (or "bugs") can cause a disease processes such as pneumonia. This concrete understanding can contribute to frightening thoughts and images, for instance, of "bugs" taking up residence in their lungs [51, 52]. *Contamination* explains disease by means of contact with something (e.g., "I have a cold because my head touched the cold winter air"). While children in this stage have a better understanding of cause and effect, their logic is usually concrete and limited to a singular etiology, which can result in fearful misunderstanding [51, 52].

Ages 11 Years and Older

During the formal operational stage, children can think abstractly and are better able to understand the processes of disease. The transition to abstract thinking also allows them to recognize themselves as separate from the rest of the world. At this stage, they employ two primary strategies to understand illness: psychophysiologic and physiologic. *Physiological* explanations of disease involve understanding how unrelated symptoms can stem from a single disease process in a systemic fashion. For example, pedal edema, shortness of breath, and chest discomfort all arise from congestive heart failure. *Psychophysiological* explanations represent the most mature understanding of disease and incorporate the influence of thoughts and feelings on body function and, ultimately, disease states (e.g., "All that stress at work caused him to have a heart attack") [43, 47]. In each of these, multiple etiologies can be considered for a disease [46]. During this stage, children are far better at understanding medical discussions, and autonomy, cosmetic implications, and lack of privacy become important issues [42].

Anxiety in any patient regardless of age is a "common phenomenon and is accepted as a normal response in anticipation of a surgical or invasive procedure" [53]. Hospitalization, especially for surgical procedures, commonly induces acute distress in a patient due to many factors including, for instance, fear of the unknown and anticipated loss of control. Anxiety can emerge immediately upon planning of a surgical procedure as the theoretical risks become more tangible, and this anxiety often intensifies upon hospital admission. Psychological manifestations of anxiety include increased worry, nervousness, and apprehension. Anxiety can result in physiological responses such as muscle tension, tachypnea, tachycardia, hypertension, sweating, nausea, and heightened sense of touch, smell, and hearing.

Common factors contributing to perioperative anxiety include concerns about the procedure itself, consequences of surgery, and the very prospect of undergoing anesthesia. The patient's own previous experience with surgery and those of family and friends can also increase levels of anxiety. Age, gender, type of surgery, previous hospital experience, vulnerability, and ability to cope with stressful experiences each influence a patient's surgery-related anxiety [53, 54]. Separation from parents and pain cause anxiety in children, whereas lack of control, fear of the unfamiliar hospital staff and environment, anesthesia, and the surgery itself can cause anxiety in children and caretakers alike [55–57]. Both children and their caretakers experience psychological distress during the preoperative period. This manifests as worry, fear, sadness, and at times even overt behavioral changes.

The psychological stress involved in anesthesia induction can lead to emotional distress and regressive behavior during recovery. Psychological reactions include nightmares, eating disorders, bedwetting, and separation anxiety [58]. Fright, anger, and feelings of helplessness may also be experienced [59]. Children with higher anxiety are at a higher risk of displaying negative behaviors after surgery [59]. Parental anxiety can amplify the child's preoperative anxiety via indirect transference [59].

Studies on the effect of parental presence in the operating room during induction of anesthesia have yielded mixed results. Early studies reported that parental presence during induction has the same or better anxiolytic effect on the child's anxiety as oral midazolam [60, 61]. However, subsequent research has failed to find a consistently positive effect [62–64]. In the most recent study to date, all children undergoing surgery received preoperative oral midazolam and were randomized to have parents present or absent during anesthesia induction [65]. The study found that the group with parental presence experienced less anxiety, suggesting a synergistic effect of midazolam and parental presence. Interestingly, in this study, presence of the parent during induction had no effect on the parent's level of anxiety, though presence during induction led to greater parental satisfaction [66].

Preoperative anxiety leads to a need for higher doses of sedatives and anesthetics, increasing risks associated with surgery. Anxiety in the postoperative period enhances the experience of postoperative pain and may lead to receipt of more pain medication, causing diminished physical activity and slowed respirations and ultimately increased pulmonary risks. Decreased activity can also result in an increased risk of deep vein thrombosis and reduced bowel transit [67, 68].

The importance of recognizing preoperative anxiety in adolescents has received limited attention but nevertheless deserves consideration because adolescents are especially vulnerable to worry, though this may be less evident to the observer than the behavioral manifestations of anxiety in younger children. Adolescents seldom self-report anxiety spontaneously and are often less likely to appear anxious due to social expectations [69–71]. Additionally, adolescents may evince less of a correlation between observable anxiety and the psychophysiological manifestations such as increased heart rate, respiratory rate, skin conductivity, and blood pressure [72]. The less-overt anxiety in the adolescent may be easily overlooked by the physician and is at risk of undertreatment. Another study of 59 adolescents ages 11–18 found that over 80% of them reported significant anxiety at the time of induction.

They also had a higher tendency toward physical manifestations of anxiety. Adolescents with somatization tendencies and fearful temperament were also prone to high levels of preoperative anxiety. Certain factors were not predictive of anxiety in the above study, such as previous surgery, birth order, attendance at preadmission visit, education level of parents, gender, number of siblings, and behavior of the adolescent during previous medical visits [69].

Adolescents who undergo repeated painful procedures may develop a conditioned anxious response to future similar procedures [73]. Thus, it is not simply a matter of whether the teenager has undergone surgery before, but also how anxious he was during his previous surgery [69]. Children and their parents need to be prepared prior to surgery to minimize the level of anxiety. Healthcare providers should anticipate anxiety in both parents and their children as a normal aspect of surgical experience [74].

Psychiatric Conditions in the Perioperative Period

Here we describe four common psychiatric conditions seen in the perioperative period. These include anxiety, depression, aggression/agitation, and delirium.

Anxiety

Anxiety is a psychophysiological reaction to perceived danger, illness, or an unknown situation [75]. Although preoperative anxiety is an expected part of the operative experience, it is a significant problem regarding health outcomes in children undergoing surgery [75–77]. Both having an illness that requires surgery and the prospect of surgery itself can cause high levels of anxiety, and this anxiety has been associated with worse surgical behavioral consequences. For instance, one study found that 54% of pediatric patients exhibited negative behavioral responses 2 weeks after surgery. These behaviors included nightmares, separation anxiety, and increased fear of physicians [78]. Even at 6 months, 20% had persistent behavioral difficulties. As one might expect, anxiety regarding surgery and associated behavioral responses differ based on child age and stage of development [78].

Assessment Tools for Anxiety

Given the known psychiatric impact of surgical procedures on children, it is important to evaluate baseline psychiatric conditions and development of the child presurgically to optimize management in the perioperative period. As a result, psychiatric assessment as part of a multidisciplinary, team-based approach should be an element in the care of children at particular risk for postsurgical psychiatric complications. A number of tools exist to define risk of psychiatric sequelae in the postsurgical period.

Tools that enable clinicians to assess presurgical anxiety, in an effort to identify children at highest risk, are important to both the management of anxiety and improvement of surgical outcomes, as well as research relating to the psychiatric implications of surgery. To that end, there has been significant work conducted to field tools that are valid and clinically applicable. A number of tools exist, including the Yale Preoperative Anxiety Scale, as well as the modified Yale scale, and others such as the State-Trait Anxiety Inventory for Children (STAIC) and the Children's Perioperative Multidimensional Anxiety Scale (CPMAS). Each of these varies in terms of methodology, with different levels of clinical validation; in addition, use of these scales over time has led to modifications and adaptations to fit specific clinical scenarios. Finally, scales must take into consideration unique pediatric populations and developmental stage. Many children under the age of 8 years cannot read; others may not be able to fully grasp or understand detailed questions.

The STAIC was long considered to be the gold standard for assessing pediatric presurgical anxiety. In many ways, the STAIC is an adaptation of a scale that was originally developed for adults: the State-Trait Anxiety Inventory (STAI). The STAI and STAIC have been employed in more than 1000 peer-reviewed studies to answer questions related to presurgical anxiety. The STAI and STAIC both have a significant shortcoming; however, they typically take 5–10 min to administer, which is not always practical in a busy preoperative holding area.

Other tools such as the Yale Preoperative Anxiety Scale (YPAS) and the modified Yale Preoperative Anxiety Scale (mYPAS) have been developed to address some of these clinical challenges, including the need for an efficient, validated scale that is practical for broad clinical use. mYPAS measures five separate domains: activity, vocalizations, emotional expressivity, state of apparent arousal, and use of parent. Within each of these categories, behavior is rated on a scale ranging from 1–4 for most items, and 1–6 for others (higher number correlates with increased anxiety). The YPAS and mYPAS were originally validated by comparing scores and outcomes to the STAIC. As time has progressed, each of these scales has undergone additional iterations and modifications, primarily geared toward improving the ease of clinical deployment. Initially, mYPAS was administered at several separate points, including, in the preoperative holding area, the walk to the operating room (OR), entrance to the OR, and introduction of anesthesia mask. mYPAS-SF is able to achieve reproducible results to mYPAS, while eliminating two of these administration sites. In addition, mYPAS-SF achieves nonstatistically different results as mYPAS with elimination of the parent use category of questioning [79].

Although significant effort has been invested in the development and validation of psychometric scales for use in children about to undergo surgery, they may be most useful for conducting studies across multiple institutions to objectively evaluate both interventions and changes in procedure to minimize anxiety. Ultimately, the clinician should use their best judgment and employ empathy as their primary tool to minimize anxiety when approaching a pediatric patient.

Scoliosis and Anxiety

Scoliosis is one of the medical conditions in which perioperative anxiety has been studied the most. One to three percent of adolescents have adolescent idiopathic scoliosis; of these, approximately 80% are female [80]. Idiopathic scoliosis is a multifactorial disorder, and it often requires surgery. Spinal fusion surgery for the correction of adolescent idiopathic scoliosis is the most extensive and invasive procedure performed in adolescents. It can result in moderate to high levels of pain [81, 82].It creates significant anxiety in the patient and their caregiver due to the complexity of the procedure, anticipation of postoperative pain, and the potential for many complications [83]. In many cases, the pain after surgery for idiopathic scoliosis is transient and limited to the immediate recovery phase. However, in some cases, the pain can persist for months or years postoperatively, which can affect the patient's everyday functioning [84, 85].

Rhodes, et al., in her article "Does Preoperative Orientation and Education Alleviate Anxiety in Posterior Spinal Fusion Patients? A Prospective, Randomized Study," examined the effects of preoperative orientation and education on alleviating anxiety on posterior spinal fusion pediatric patients and their caregivers. Patients between the age of 11 and 21 undergoing elective posterior spinal fusion (PSF) between May 2010 and November 2011 were identified and randomly distributed into 2 groups, a control group ($N = 39$) and interventional group ($N = 26$) [83]. In this study, patients and their caregivers' anxiety was measured pre- and postoperatively. The intervention group received extensive preoperative education and orientation for scoliosis surgery (PEOSS). PEOSS included an informational session, a tour of the hospital and information about pain. The intervention group had higher patient satisfaction scores than controls; however there were no significant differences between the groups in regard to the level of pain, morphine requirements, or length of stay. The anxiety level was higher in the PEOSS group than in the nonintervention group.

In another prospective study, LaMontagne et al. implemented an intervention that included preoperative education and coping skills training. This intervention found something that coping skills training decreased postoperative pain, which is related to anxiety [86]. The study suggests that, although specific and accurate medical information is important, it must be balanced with coping skills in order for patients to handle the information. Providing adolescents with coping skills is important because their anxiety is underestimated due to their use of the coping mechanisms of withdrawal and an uninterested attitude. This observation is supported by other studies, as we have already seen [69]. Providing coping skills throughout their hospital stay, not just during the preoperative period, is beneficial to the adolescent patient.

Depression

Little research has addressed the impact of depression on the presurgical pediatric patient. A primary concern is how and when to hold versus continue antidepressants, particularly in individuals with depression or bipolar disorder for whom a stable regimen has been identified. For adults, multiple studies have explored the perioperative risks of selective serotonin reuptake inhibitors [87], in particular the risk of intra- and postoperative bleeding in patients taking SSRIs [88]. To our knowledge, there is no specific information about the use of SSRIs perioperatively in the pediatric patient.

On the other hand, monoamine oxidase inhibitors (MAOIs) carry identifiable risks when combined with several agents used during anesthesia, including meperidine, dextromethorphan, and direct and indirect sympathomimetics. For elective surgeries, it is recommended to discontinue MAOIs for 14 days prior to elective surgeries, when possible [89]. Similarly, tricyclic antidepressants (TCAs) may be withheld 7 days prior to elective surgery [89]. Antidepressants can then be restarted as soon as possible postoperatively, once the patient is no longer expected to require anesthetic agents.

Aggression and Autism Spectrum Disorder

Aggression may be a feature of autism spectrum disorder (ASD), developmental delay, attention-deficit/hyperactivity disorder (ADHD), and oppositional defiant disorder. In this section, we focus on ASD due to its complexity and the treatment challenges it presents.

ASD is a neurodevelopmental disorder diagnosed in more than 1 per 100 children in the USA. It is characterized by impairment in social communication (such as an inability to understand facial expression, respond to social cues, understand body language, and use social language) and repetitive behaviors. Children with ASD may also exhibit sensory abnormalities including hypersensitivity to touch, visual stimuli, sounds, and taste. Among children with relatively higher IQ, males are 4–9 times more likely to be affected than females; among those with lower IQ, the male-to-female ratio has been reported in the range of 1.3–2.4 [90, 91]. More than half of children with ASD have intellectual disability with an IQ < 70 [92].

Delirium

Pediatric delirium is an underrecognized but serious disorder present in many postoperative patients. Its symptoms are often difficult to assess due to the varying communication and developmental abilities in children and adolescents. However, recently validated rating scales for pediatric delirium allow for more reliable assessment of this condition. Familiarity with the varied presentation of pediatric delirium, routine use of valid rating scales, and instituting best management are imperative for good care. Missing this disorder is associated with increased rates of morbidity and mortality as well as other traumatic sequelae such as the development of posttraumatic stress disorder.

Because it remains unclear how the presentation of pediatric delirium may differ from delirium in adults, we rely on descriptions in the adult literature. Delirium affects both consciousness and cognition with the cardinal features being acute change in mental status that tends to fluctuate, impaired attention, reduced awareness of one's environment, and appreciable cognitive impairment [93]. For a detailed discussion about the pathophysiology of delirium, please refer to Chap. 4 "Delirium."

In the perioperative setting, delirium is often parsed into two general categories: general and emergence delirium [94]. *Emergence delirium* (ED) is a change in cerebral dysfunction that occurs after emerging from anesthesia and can continue into the recovery period. It is typically reported to last 45 min to 1 h post-anesthesia and often defined by agitation with kicking, absence of eye contact, inconsolability, and absence of awareness of surroundings. *General delirium* (GD) represents a change in mental status not associated with anesthesia. Despite this distinction made by some, the syndrome is clinically the same, and management is therefore identical.

The reported incidence of pediatric delirium varies widely, from 10% to 80% [95]. This imprecise range speaks to the variability in awareness and assessment of this condition. Importantly, agitation related to postoperative pain should be distinguished from delirium and treated appropriately.

Assessment Tools for Pediatric Delirium

Pediatric delirium continues to be vastly underrecognized and underdiagnosed. There are many challenges associated with making this diagnosis, including the inherent difficulty in assessing nonverbal or preverbal children, the subtle symptoms that can vary depending on developmental stage – itself further complicated by developmental variability – and the similarity in symptoms associated with pain, distress, and medication withdrawal [96].

Although identification of delirium in children can be difficult, there are now several valid, reliable assessment tools to identify this disorder. They include:

1. The Pediatric Anesthesia Emergence Delirium Scale [97]
2. The Pediatric Confusion Assessment Method for ICU [98]
3. The Cornell Assessment Pediatric Delirium tool [99]
4. The Sophia Observation Withdrawal Symptoms Pediatric Delirium scale [100]

The similar sensitivity (83–94%) and specificity (79–98%) across screens have led to the overall conclusion that the choice in screen is user-dependent. It is important to note that serial assessments are necessary as delirium, by definition, tends to fluctuate [101]. After obtaining a positive screen, the clinician should identify the cause for the child's symptom [94]. A positive delirium screen may be due to a somatic complication, medication effect, or physical discomfort [102] (Table 15.1).

Risk Factors for Pediatric Delirium

Several risk factors for delirium have been reported, including age, sex, preoperative anxiety, and type of surgery and anesthesia used during the surgery [104]. Several studies of pediatric delirium suggest that preschool-age children 2–6 years of age are at the greatest risk of delirium, with a postoperative incidence of 30–50%. This delirium risk decreases into adulthood where risk is between 4% and 20% [95]. Other studies find that male children of preschool age are at a greater risk (40%) than their in-school peers (11.5%) [96].

Inconsistent evidence suggests that ear, nose, and throat surgeries may be associated with a greater risk of delirium. Certain anesthetics including sevoflurane, desflurane, and isoflurane have also been shown to increase the risk of ED. The cause of this increased ED risk is unclear. Oral administration of anesthesia has been associated with greater risk of ED relative to intravenous anesthesia administration; however, the rate of emergence, anesthesia duration, and depth of anesthesia do not appear to alter ED risk. A meta-analysis recently concluded that propofol may decrease the risk of developing ED [105].

Preoperative anxiety has been proposed as a risk factor for postoperative delirium. It is associated with parental anxiety, young age, few siblings, poor sociability, poor social adaptive capabilities, poor quality of previous medical experience, and low rating for activity [104]. As with other risk factors for pediatric delirium, the data implicating preoperative anxiety and delirium is inconsistent. For instance, one study found that for every ten points higher on the modified Yale Preoperative Anxiety Scale, the risk of ED increased by 10%. However, subsequent studies found no such relationship [106].

Clinical Features of Pediatric Delirium

Clinical features of pediatric delirium include irritability, agitation, sleep-wake disturbance, emotional lability, and fluctuation of symptoms. Symptoms less commonly observed in the pediatric population when compared to the adult population include hallucinations, delusions, memory impairment, and speech disturbances. Other unique features of pediatric delirium include developmental regression with loss of previously acquired skills, inability of the usual caregiver to console the child, and reduced eye contact with the usual caregiver [107].

Interestingly, decreased eye contact with caregiver and non-purposeful movement have been found in association with pediatric delirium but not in agitation secondary to postoperative pain. Thus, these may be important distinguishing features between the two often confused conditions [108].

Similar to adult delirium, pediatric delirium presents with a wide range of symptoms and a continuum of psychomotor behavior categorized as hyperactive, hypoactive, or mixed level of activity. Hyperactive delirium presents with restlessness, agitation, and emotional lability. These patients are often at greater risk for self-harming behaviors such as self-extubation. Hypoactive delirium presents with apathy, decreased responsiveness, and withdrawal. This type of delirium is commonly missed or misdiagnosed as depression. Though data in children are lacking, the

Table 15.1 Common pediatric delirium screens characteristics [103]

	The Pediatric Anesthesia Emergence Delirium Scale (PAED)	The Pediatric Confusion Assessment Method for ICU (pCAM-ICU)	The Cornell Assessment Pediatric Delirium tool (CAP-D)	The Sophia Observation Withdrawal Symptoms Pediatric Delirium scale (SOS-PD)
Symptoms assessed	Eye contact with caregiver Purposeful actions Awareness of surrounding Restlessness Inconsolability	Acute change or fluctuating course of mental status Inattention Altered level of consciousness Disorganized Thinking	Eye contact with caregiver Purposeful actions Awareness of surroundings Ability to communicate needs Restlessness Inconsolability Under-activity Response to interaction	Tachycardia Tachypnea Fever (≥38.5 °C) Sweating Agitation Anxiety Tremors Increased muscle tension Inconsolable crying Grimacing Sleeplessness Motor disturbance Hallucinations Vomiting Diarrhea[1]
Sensitivity	91%	78%	79%	97%
Specificity	98%	99%	94%	92%
Time to complete		2–4 min	<2 min	
Pros	Useful in all ages Useful in nonverbal children	Widely used	Widely used Captures hypoactive and mixed type delirium Useful in all ages Useful in nonverbal children	Useful in all ages
Cons	Limited for use in the hyperactive subtype of delirium	Requires patient cooperation Restricted to children more than 5 years old Limited in patients with developmental delay Requires extensive nurse training	Requires some training including understanding of "anchor points"	Does not capture hypoactive delirium
Age group	1–17 years	> 5 years	0–21 years	0–16 years
Score range	0–25 [10]	Positive if 1, 2 and 3 or 4 present	0–40 [9]	0–15 [4]
Reliability	+	+	+	+/−
Forms of validity established	Criterion	Criterion	Criterion	Face (criterion pilot)

adult literature has found that hypoactive delirium is much more common than hyperactive: 43.5% vs 1.6%, respectively [109]. Delirium with mixed level of activity is often cited as the most frequent presentation at 54.1%. Nevertheless, transition from one motoric subtype of delirium to another is common due to the fluctuating nature of this condition.

Biomarkers of Pediatric Delirium

Though there has been research investigating the role of biomarkers for delirium, the results remain limited. Preliminary candidate biomarkers have included hemoglobin-beta, S100 calcium-binding protein B, and IL-6. The EEG has also been considered but has yet to demonstrate features unique to delirium. At best, non-specific diffuse wave slowing is found in 65–86% of pediatric delirium cases. Given the limitation of understanding these adjunctive tests, pediatric delirium remains a clinical diagnosis [110].

Treatment of Perioperative Psychiatric Conditions

Non-pharmacological Treatment

Experiencing surgery can be stressful for both pediatric patients and their families. Children can feel afraid of the unfamiliar routines that occur at the hospital such as checking vital signs, inserting IV access, or blood drawing. Also the sounds of the monitors or lights, smells, and clothing can be unfamiliar and stressful. Nurses and physicians caring for children in various developmental stages should be prepared to provide developmentally appropriate care to alleviate anxiety experienced by the patients and their caregivers [103].

It is important to allow time to prepare the child and the parents as such preparation has been shown to decrease anxiety, which can later prevent negative outcomes after surgery such as negative behavioral changes and postoperative pain. Many children's hospitals and pediatrics departments have child life specialist that provide surgical preparation for children prior to surgery or other procedures. The child life specialist also helps the patient and the parents to cope with the experience. The child life specialist often meets with the child and the family during the preoperative visit and explains the anesthesia and the surgical procedure in developmentally appropriate terms. In small hospitals or ambulatory surgery centers where the child life specialist may not be available, the preoperative nurse will take on the role to explain to the child and the family the nature of the procedure to decrease anxiety and fears.

The child life specialist, as well as the nurse, must be aware that preoperative preparation relies on developing a collaborative relationship with the parent or other caregiver as they know the child, and her temperament, and can normalize the hospital environment for the child and decrease her fears [111]. Multiple instruments can be used to help children understand the surgical procedures and the hospital environment and routine. Some of these items include stethoscopes, blood pressure cuffs, EKG pads, anesthesia masks, IV tubing, books, and pictures.

Preparing the Infant and Toddlers

Since infants and toddlers are unable to comprehend preparation for surgery and thus will not benefit from it, the preparation involves the parents only. Infants and toddlers require the parents' presence for reassurance, for meeting their needs, and for soothing with a pacifier, blanket, and/or a stuffed animal. Infants and toddlers learn and interact with their environment through senses and motor movements; therefore, the use of music or toys can distract them, which allows for preparation necessary prior to a procedure [103].

Allowing toddlers to enjoy, manipulate, and handle medical equipment may assist with relieving their anxiety and with gaining trust and cooperation [103, 112]. For example, letting a toddle place a blood pressure cuff on and then hold it and play with it while the nurse is getting the reading could be helpful. Separation anxiety can be difficult for a young child so keeping the parents nearby as permitted is also important. Rewarding the toddler patient with an inflated glove or a sticker is helpful to avoid unpleasant memories. Undergoing surgery and admission to the hospital postoperatively can lead to disruption in the sleeping and feeding routine of the toddler; thus, helping the parents cope with this disruption with adequate preparation is beneficial.

Preparing Preschoolers for Surgery

Children between the age of 2–5 years old are verbal and can misinterpret words that require abstract thinking, leading to anxiety and fears. It is important to assess this age group by sitting at the child eye level and have the parent physically close, by holding the child, to enhance cooperation. Sitting on the parents' lap, for example, while the nurse or the physician to examine the child at eye level is preferred, if possible. It will be helpful to elicit from the child the reason she came to the hospital and determine the level of understanding. "I understand that you came today because you have jumped and cut your leg." In addition to using terms that are easily understood by the child, it is also important to use the correct anatomic term for the body part and medical equipment involved in the procedure. For example: "This is a pulse oximeter, it has a red light, and I will put it on your finger and check the oxygen in your body."

Children in this age group tend to be frightened due to separation from their caregiver, and the nurse should encourage the parents to remain with their child as much as medically possible. It will be appropriate to give the parents and the child a surgical hat and gloves to normalize the environment. Also it is important to tell the child that when the doctor will work on the body part he or she will be asleep and will not feel anything. To help the child to feel comfortable in the hospital environment, she can bring a toy or stuffed animal, and the nurse or physician can use the stuffed animal as a model for demonstrating the procedure or medical act, for example, listening to the stuffed toy's heart. The medical staff should not forget to ask permission from the child to listen to or manipulate the toy; they should also reinforce that the toy will get better.

Preparing School-Age Children

Children in this age group are between 6 and 11 years of age, and separation from parents is easier for them [113]. They are also able to understand the medical concepts of their illness and the surgical procedure [42]. It is important to elicit their knowledge by asking "Tell me what you know about why are you here today?" or "What brought you to the hospital today?" Directing the question to the child and not to the parent gives the child the opportunity to express herself. This is important because children often hear about the procedure or surgery from the media or friends, and this can lead to misconception or incorrect information. Children often worry about not waking up from anesthesia simply because they may have heard stories about it. Children in this age are also afraid of the unknown, illness, and body harm, and allowing them to express this is important. Children in this age may hear "After anesthesia you will not remember anything," which they can interpret as "I will not remember my name, address or my family"; reassurance and explanation is crucial.

Pictures from a simple anatomy book that allow the young reader to visualize the information can be helpful in preparing school-age children for surgery, since it enhances their understanding of body parts, systems, the location of the affected organ, and surgical site. Allowing the child to participate in her care often leads to better cooperation [103]. An example would be to say: "I need to check your temperature and listen to your heart. What would you like me to do first?" In this way, the hospital staff can enhance the child's feeling of mastery and cooperation. Allow the child to perform simple tasks after surgery can also increase the child's involvement in her care. Asking the child about coping with a situation and giving him/her options can increase their independence, for example, "Would you like to watch me place the IV, or would you like to look away and listen to music while I place the IV."

Preparing Adolescents for Surgery

Patients in the adolescent age group fear loss of self-control and autonomy [114]. As a result, they may demonstrate an oppositional attitude when being told to wear a hospital gown, remain NPO, or discuss private issues. They may withdraw or not cooperate with the medical staff. When treating adolescents, it is important to address the adolescent and not the parents to affirm their independence [42]. Most adolescents can provide adequate and accurate history including past medical history, psychiatric history, allergies, and medications used. If the adolescent is uncomfortable, the parents can assist.

Allowing the adolescent to communicate with their peers via phone or social media can help to distract the adolescent and thereby normalize the situation, resulting in reduction in both the anxiety and the need for anxiolytic medications [114]. Adolescents are often concerned with altered body image and cosmetic effects following surgery [42]. They worry about scars and peer rejection as a result of the surgery. Validating the adolescent's concerns without judgment and minimizing their fears can lead to a decrease in anxiety and an increase in cooperation.

Preparing Children with Developmental Delay (DD) or Autism Spectrum Disorder (ASD)

Preparing children with DD or sensory processing disorders, such as ASD, can be challenging. Children may have different levels of deficits involving one or more domains of development. Some children may have deficits in social interactions or language; others can have significant cognitive delays. Children or adolescents with ASD tend to be concrete and may not understand abstract thoughts. These patients are usually more sensitive to light, noises, and unfamiliar environment, which can result in fears, mood dysregulation, and aggression [115]. Children with ASD can exhibit an increase in temper tantrums and self-injurious behaviors – such as head banging and hitting – putting themselves and medical staff at risk [115]. Planning the care prior to surgery is important for these children to minimize distress. The following information may be helpful to nursing and medical staff taking care of ASD patients perioperatively:

1. The level of the child's understanding of the procedure
2. The ability of the child to communicate verbally
3. The ability of the child to tolerate transition
4. Techniques or strategies that worked in the past to overcome the anxiety related to past procedures

ASD is associated with increased risk of medical and surgical illness. For instance, children with this condition may suffer injuries because of falls or head trauma due to either high-risk or self-injurious behaviors. They are also at risk of medical conditions such as bowel obstruction from chronic constipation. Lack of knowledge of ASD and its associated psychological and behavioral features places this group of patients at greater risk of adverse events during medical hospitalization and especially during procedures. Understanding ASD and its manifestations will assist the team in planning of both the surgery and the perioperative period with the goals of mitigating patient discomfort, reducing care burden of staff, and ensuring the safety of patients, caregivers, and staff.

To avoid adverse events, the diagnosis of ASD should be identified prior to surgery, and adequate preparation of the parents and staff should occur. Children with ASD and normal intelligence tend to have fewer adverse events due to their ability to understand and participate in care. Both stories and videos may assist in preparing the patient and caregiver for surgery. It is important to keep the admission time flexible, and waiting time should be minimized. If possible, the child with ASD and their caregivers should be placed in a quiet room to decrease stimulation to the child. Additional non-pharmacological considerations include (Table 15.2):

Table 15.2 Additional non-pharmacological considerations in ASD

Unless necessary, do not dress the child in a hospital gown
Allow the family to bring familiar items from home (e.g., a phone, favorite toy)
Avoid topical analgesic cream if it is distressing to the child
Obtain as much admission information from the parents as possible

Non-pharmacological Interventions for Anxiety in Children

There are multiple techniques available to help children cope with preoperative anxiety. These include progressive muscle relaxation (PMR), autogenic training, and guided imagery. PMR is a technique that consists of alternating flexing and relaxing of the muscles of the legs, abdomen, chest, arms, and face. This type of exercise is helpful in reducing pain, pain perception, and tension. It also creates a peaceful and pleasant state that helps to reduce anticipatory anxiety, including preoperative anxiety. The mechanism involves decreasing parasympathetic activity.

It also increases feelings of control, improves the patient's ability to block inner thoughts, improves sleep, decreases cardiac index, lowers blood pressure, warms or cools body parts, and enhances performance of physical activity. This exercise should be performed three times a day for 15–20 min prior to surgery [116].

Another technique to aid in reducing preoperative anxiety is autogenic training. This involves the individual learning a set of directions/exercises to command the body to relax and control breathing, blood pressure, pulse, and temperature. This technique uses visual imagination and verbal cues. It requires 4–6 months to master.

Guided imagery is another technique to reduce preoperative anxiety. The patient spends 10 min of practice a day, imagining images that are symbolic in the patient's life of a safe and comfortable place, such as a beach or forest. All the senses are used to create a rich experience. It is a very useful technique preoperatively to reduce anxiety [117].

Interventions for Pediatric Delirium

There are several options for non-pharmacological management of pediatric delirium which in our opinion should be implemented for any child suspected of delirium. These measures are summarized in Table 15.3.

Pharmacological Treatment

Anxiety

To help children cope with perioperative anxiety, multiple pharmacological agents are available. In addition, sedatives used in anesthesia can be used to help with sedation, anxiolysis, and amnesia. Analgesics can be utilized to reduce pain.

Studies show that in children with behavioral problems – such as ADHD, autism, developmental delay, oppositional defiant disorder, and anxiety – a combination of pharmacological and non-pharmacological techniques work better versus non-pharmacological treatment alone [118].

Another study, ADVANCE, a preoperative program designed for pediatric patients to diminish psychiatric perioperative complications, demonstrated that interventions such as anxiety reduction, distraction, and video modeling and education, to name a few, helped to lower anxiety in the preoperative period. It also proved to reduce delirium, analgesic requirements, and hospital stay. However, the same study found that administering oral midazolam yielded the same result and was equally effective in reducing preoperative anxiety [119].

When given, premedication should be safe and effective. The oral route is preferred [120]. The most common premedications are benzodiazepines, with midazolam being the most

Table 15.3 Non-pharmacological interventions for pediatric delirium

Environmental modifications	Create a calm and predictable environment by having familiar items in the room including favorite toys, blankets, music, pictures, etc.
	Have children with glasses or hearing aids wear their devices
	If a child has hypoactive delirium, put them in a room near an active area of the unit
	If a child has hyperactive delirium, put them in a room in a quieter part of the unit
	Do not use physical restraints unless absolutely necessary
Encouragement of normal sleep cycle	Disruption of sleep quality and duration are associated with the development of delirium. The following strategies are often found helpful in maintaining a normal sleep cycle.
	Have a consistent daily schedule for each postoperative patient. This should include a consistent wake up time as well as time out of bed during the day
	Avoid daytime sleeping if possible
	Open up the curtains during the day or, if not near a window, use a dimmer to stimulate a lighted environment during the day and a dark environment at night
	Frequently reorient the child to the date, time, and place
Family involvement	A stable presence of a parent or caretaker has been shown to be extremely helpful in preventing and improving delirium
	The family member should be educated on delirium as this can often be a frightening experience

common, as it has a rapid onset, short duration of onset, and relatively few side effects [121]. Benzodiazepines activate the GABA receptor and have an inhibitory effect on neurons. The dose range of oral midazolam is between 0.25 and 1 mg/kg; the maximum daily dose is between 15 and 20 mg. Peak effect is seen in around 20–30 min. The dose range of the parenteral form is much lower (0.2–0.03 mg/kg) and obviously has a more rapid time to peak effect. Midazolam can also be given intranasally using an atomizer. Midazolam side effects include disinhibition and dysphoria [122]. Rarely, it can cause paradoxical excitement: this type of response has been called "angry child syndrome."

Other benzodiazepines like diazepam and triazolam have also been used in surgical procedures. Diazepam produces good skeletal muscle relaxation and anxiolysis.

Ketamine is a sedative and analgesic and has been found to be effective in autistic children, as already noted above [123]. It can be given intramuscularly in a dose range of 3–5 mg/kg. Its onset of action is 5 min and its duration of action is roughly 45 min. Ketamine causes less respiratory depression compared to midazolam, but its side effects include hallucinations and emergence delirium [123]. In milder cases of autism, oral midazolam is preferred; oral ketamine is preferred in moderate to severe cases. Combination of midazolam and ketamine has also been in used in difficult children [121].

Alpha agonists like clonidine have also been used in dosing ranges of 2–4 microgram/kg to help with anxiety and sedation. Clonidine has been reported to be helpful in autistic children [124]. Dexmedetomidine is a selective alpha-2 adrenergic agonist and has been used successfully in dosage ranges from 1 to 4 microgram/kg, even in patients with failed sedation [125]. It causes minimum respiratory depression and is considered to be a relatively safe drug [126]. Caution should be used in patients with bradycardia and AV block, as dexmedetomidine may depress SA and AV node conduction in children [125].

Intranasal dexmedetomidine at doses of 2.5 microgram/kg produces more sedation, while midazolam produces more amnesia. One meta-analysis reported by Peng et al. reported that dexmedetomidine is superior to midazolam premedication because it resulted in enhanced preoperative sedation and decreased postoperative pain [127]. The use of dexmedetomidine preoperatively has been found to reduce the incidence of delirium, while midazolam has the propensity to induce delirium. Finally, antihistamines have also been used adjunctively with other sedating agents. Common agents used are hydroxyzine, promethazine, and diphenhydramine.

Autism Spectrum Disorder

The use of medication preoperatively is recommended for children with ASD, ADHD, developmental delay, and oppositional defiant disorder (ODD). These include the following.

Midazolam It can be used successfully in patients with mild forms of autism.

Ketamine Oral ketamine may be considered as an alternative to midazolam, especially for the uncooperative, intellectually impaired child. Adverse effects may include nausea and vomiting, nystagmus, hypersalivation, vivid dreams, sensory and perceptual illusions, disorientation, emergence phenomena, or rare laryngospasm. Emergence phenomena are not associated with dosage and are more common in females, rapid intravenous administration, and excessive noise during recovery. Emergence phenomena are also less frequently seen in children younger than 15 years and children placed in a dark room [128].

Alpha-2 Agonists Both clonidine and dexmedetomidine may be considered for sedation in children. Oral clonidine 2–7 microgram/kg causes sedation in an hour (average 58 min, range 35–135 min). One in six children may experience a mild decrease in blood pressure and heart rate [124]. Dexmedetomidine has been studied for procedural sedation in children undergoing MRI or EEG. In one study, 83% of children with ASD and 99% of children with other neurobehavioral disorder achieved sedation [126].

Risperidone Low doses of the antipsychotic agent risperidone may be considered to manage agitation in the perioperative period. In general, for those children who are on an antipsychotic at home, changing a psychotropic regimen during the perioperative period should be done very cautiously to prevent psychiatric decompensation. Continuing a home antipsychotic agent throughout the perioperative period is usually tolerated, though occasionally an antipsychotic with a shorter half-life or reduced dose may be considered [129, 130].

Psychostimulants Children on a psychostimulant may require higher doses of sedation during anesthesia and may be at increased risk of hypertension and arrhythmias. Psychostimulants can also interact with vasopressors [131]. When methylphenidate and halogenated agents are used together, they increase the risk for hypertension. It is recommended to withhold psychostimulants the day of surgery [132].

Selective-Serotonin Reuptake Inhibitors (SSRIs) The risk of continuing SSRIs in children during the perioperative period remains controversial. Some authors recommend discontinuing SSRIs in the perioperative period due to the slight but nevertheless non-negligibly higher risk of bleeding; others recommend continuing SSRIs during this time in all patients except those having major CNS procedures, because they can increase the risk associated with transfusion secondary to reduced platelet aggregation, especially if used concomitantly with NSAIDs [90].

Pharmacological Interventions for Pediatric Delirium

The optimal management of pediatric delirium is three pronged [101]. The first prong is a thorough assessment to identify the underlying cause of the delirium. As this book is geared toward perioperative care, the most likely cause of the delirium will be a postanesthetic reaction. However, it is important to rule out other factors that could be leading to the delirium, including hypoxia, medications such as anticholinergics and benzodiazepines, metabolic disturbances, pain, and anxiety. Treatment of the underlying cause, if there is one other than the anesthesia emergence effect, will result in a rapid reduction or complete resolution of symptoms. Next, supportive management should also be considered including early mobilization, careful management of fluids and nutrition, as well as DVT prophylaxis. Lastly, one must treat the symptoms of delirium. This can be done both via non-pharmacologic and pharmacologic methods [110].

When the above factors have been optimized and the child continues to have persistent and severe symptoms that impose a safety concern, antipsychotic medications are recommended. Though there are no FDA-approved treatments for delirium, antipsychotics have been shown to be clinically effective in pediatric delirium [101].

There are currently no formal guidelines as to the selection and dosage of antipsychotic in the pediatric population, and their use appears to be largely based on institution and clinician preference. However, in general, atypical antipsychotics are preferred due to their lower likelihood of extrapyramidal side effects. Overall, the most commonly used agents include risperidone, olanzapine, and haloperidol. Risperdal is often preferred because of its multiple delivery forms including liquid, tablet, and disintegrating tablets. Haloperidol, which can be given orally and IV, is often used for children that cannot tolerate oral medication [110].

Though atypical antipsychotics have a more favorable side effect profile than typical antipsychotics, both have possible side effects, such as tachycardia, hypotension, laryngospasm, sedation, anticholinergic effects, extrapyramidal movement disorders, tardive dyskinesia, neuroleptic malignant syndrome, malignant hyperthermia, cholestasis, and glucose dysregulation [110]. EKG monitoring for QTc prolongation is now a part of the routine care when using antipsychotic medications, although there are no guidelines as to how often EKG should be performed when treating delirium in children. As a general principle, starting the medication at the lowest dose possible, titrating only to effect, and avoiding anticholinergic medications such as diphenhydramine, can reduce the risk of side effects.

Pharmacological Management of Postoperative Pain

Assessing postoperative pain is important and can be difficult especially in young children and in children with disabilities. Untreated pain cannot only lead to behavior problems, but also delay healing of wounds and lead to a longer rehabilitation period. Treating pain adequately is an important aspect of behavior management. Premedication with sedatives and analgesics may help reduce the distress associate with pain. Perioperative pain is usually treated with multimodal analgesia, which includes NSAIDs. For severe pain management, long-acting intravenous opioids like morphine are used. Regional analgesia can provide pain relief by itself or may also help decrease the patient's opioid requirements.

Conclusion

Surgery can be an extremely stressful experience for children and their caregivers; it can lead to anxiety and fear. Understanding the psychological impact of surgery in the context of the pediatric patient's developmental stage is necessary to minimize or overcome these unpleasant experiences. Regardless of the type of surgery, preparation—either non-pharmacological or pharmacological—is important to reduce anxiety, aggression, and delirium in this patient population, with the goal of preventing lasting emotional trauma. The medical team should work with children and their families to incorporate this understanding in order to maximize the successful outcome of the surgery performed.

Take-Home Points

- Psychological preparation for surgery is essential in children and adolescents in order to reduce the emotional impact of the procedure and hospitalization.
- A significant proportion of surgeries performed in children address chronic congenital problems, therefore psychological response to surgery must be considered within the continuum of lifelong coping with illness.
- Delirium can be best recognized by using validated and reliable bedside tools.
- The management and treatment of pediatric delirium should be done via a multipronged approach which involves addressing the underlying disease, supportive care, and both pharmacological and non-pharmacological treatment.

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