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REGENERATIVE PAIN AND MEDICINE/INTERVENTIONAL PAIN AND MEDICINE (EC BRADLEY, SECTION EDITORS)

Enhanced Recovery After Surgery: Opioid Sparing Strategies After Discharge: A Review

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Abstract

Purpose of Review Many surgical subspecialties have developed enhanced recovery after surgery (ERAS) protocols that focus on multimodal analgesia to limit opioid use during a hospital stay and improve patient recovery. Unfortunately, ERAS protocols do not extend to post-discharge patient care, and opioids continue to be over prescribed. The primary reason seems to be a lack of good quality research evaluating extended use of a multimodal analgesic approach. This review was undertaken to evaluate available evidence for non-opioid analgesics in the postoperative period after discharge, utilizing Pubmed, Scopus, and Google Scholar.

Recent Findings Several studies have explored strategies to reduce the overprescribing of opioids after surgery without worsening postoperative pain scores or complications. However, these studies do not necessarily reflect on situations where an ultra-restrictive protocol may fail, leading to breakthrough pain. Ultra-restrictive opioid protocols, therefore, could risk undertreatment of acute pain and the development of persistent post-surgical pain, highlighting the need for a review of non-opioid strategies.

Summary Our findings show that little research has been conducted on the efficacy of non-opioid therapies post-discharge including acetaminophen, NSAIDs, gabapentin, duloxetine, venlafaxine, tizanidine, valium, and oral ketamine. Further studies are warranted to more precisely evaluate the utility of these agents, specifically for their side effect profile and efficacy in improving pain-control and function while limiting opioid use.

Keywords Acute pain · Postoperative pain · Non-opioid analgesics · Multimodal analgesia · Enhanced recovery after surgery (ERAS) · Discharge

Introduction

An estimated 48 million surgeries are performed in the USA annually [1]. A third of these patients have moderate to severe postoperative pain in the first 48 h, even after ambulatory surgery [2]. While multimodal analgesic use has become widespread, opioids remain the mainstay for pain management after major surgeries [3]. Many surgical subspecialties have adopted enhanced recovery after surgery (ERAS) protocols to limit perioperative opioid use and improve patient recovery within the last decade. ERAS protocols focus on multimodal analgesics that target different pain pathways. Medications are administered preoperatively, intraoperatively, and immediately postoperatively to reduce postoperative opioid consumption and reduce the duration of hospitalization [4]. These strategies also aim to minimize opioid-related adverse effects such as sedation, nausea, vomiting, ileus, respiratory depression, and pruritus. Unfortunately, ERAS protocols often do not extend to post-discharge patient care, and many surgical patients are still prescribed excessive amounts of opioids at discharge [5, 6]. The primary reason seems to be a lack of good quality research evaluating extended use of a multimodal analgesic approach.

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Large numbers of opioids prescribed at discharge may result in the issue of leftover pills contributing to opioid diversion. In this regard, every state in the USA has passed legislation to limit the amount and duration of opioids postoperatively to decrease opioid addiction and its associated morbidity and mortality. Some studies suggest that patients take only 28% of the opioids prescribed at discharge [6]. Again, the reason being limited evidence on appropriate opioid dosing for adequate postoperative pain management and optimal recovery. Research is even more lacking in the realm of non-opioid analgesics in the postoperative period after discharge.

Some studies have explored strategies to reduce opioid prescriptions at discharge, concluding that ultra-restrictive protocols are feasible without increasing postoperative pain or refill requests. However, most of these studies fail to address managing pain adequately if this strategy fails, for example, in patients who may be opioid-tolerant or undergoing major surgery with significant postoperative pain states. Although feasible, in the absence of well-defined guidance on optimal utilization of non-opioid analgesics, ultra-restrictive opioid protocols may risk undertreatment of acute pain, especially after more painful surgeries such as orthopedic, spine, thoracic, and open abdominal surgeries. Inadequately managed acute postoperative pain not only has many physiological and psychological consequences [7] but can also evolve into chronic pain, with literature suggesting persistent pain to affect between 10 and 60% of surgical patients [8–10]. The resultant persistent postoperative opioid use is a common and underappreciated surgical complication, occurring in 5.9% of patients undergoing minor surgeries and 6.5% patients undergoing major surgeries [11]. From a neurobiological perspective, anyone who continues to take exogenous opioids for an extended period will shut down endogenous opioid production, e.g., endorphins, enkephalins, and dynorphins, resulting in physical dependence on exogenous opioids. In the setting of prolonged exogenous opioid use, cessation results in central nervous system hyperarousal or what we commonly describe as a constellation of signs and symptoms termed withdrawal. Therefore, extended post-surgical opioid use could be considered a "gateway" to chronic opioid use, providing a strong justification to limit perioperative opioids, especially as the United States grapples with its worst opioid epidemic in history.

A gap exists between optimal opioid-sparing analgesia in the hospital setting and at discharge. Perioperative multimodal analgesics implemented as part of ERAS protocols have extensive evidence supporting their role in improving patient outcomes immediately postoperatively. However, research evaluating an "extension of ERAS" into the discharge phase is lacking.

Therefore, in the present investigation, we evaluated evidence of the efficacy of non-opioid analgesics in the postoperative period after discharge.

Methods

A comprehensive literature search was performed using PubMed, Scopus, and Google Scholar. Since the first ERAS protocols were implemented in the early 2000s, we limited our search to the last 20 years to evaluate the most recent evidence for the present investigation. We used the search terms "postoperative pain" AND "non-opioids" AND "discharge" in our searches. The search was limited to the English language and returned over 500 results. All relevant studies about the utilization of non-opioid analgesics for postoperative pain management were reviewed. Individual searches were also conducted for the various drugs using the search terms "postoperative pain" AND "drug name" AND "discharge" in the evaluation process. Articles that did not investigate non-opioid analgesics beyond the inpatient phase were excluded.

Results

Overall, studies exploring the benefits of non-opioid analgesics in the discharge phase are limited, especially compared to the amount of literature for these drugs in the immediate postoperative period. Non-opioid analgesics are well known for their opioid-sparing effect with improved outcomes, when used immediately postoperatively in the inpatient setting. However, most recommendations by major pain societies for managing acute postoperative pain at discharge focus on opioid prescriptions, e.g., how to screen patients before prescribing, how much to prescribe, and for how long. The American Pain Society guides the inpatient management of pain with opioids and non-opioids. They recommend instructing patients on opioid use during the transition to outpatient care but otherwise give no recommendations on the type or duration of analgesia, specifically about non-opioids [12]. The American College of Occupational and Environmental Medicine's opioid treatment guidelines include guidelines for screening patients who continue opioid pain medications beyond the second postoperative week, prescribing a maximum daily dose of 50 mg morphine equivalent in opioid-naive patients, and discontinuing opioids in patients who have reached the maximum daily dose of 50 mg morphine equivalent [13]. The Institute for Clinical Systems Improvement recommends limiting initial postoperative prescriptions to 3 days or 20 tablets with appropriate adjuncts, education, and follow-up, without regard for the type of procedure performed [14]. There are relatively few

efforts to inform providers of evidence-based prescribing guidelines in the postoperative outpatient setting for non-opioid analgesics, perhaps related to the lack of good quality literature in this realm.

Several classes of non-opioid agents that target pain via different pathways have been evaluated as postoperative analgesics. The following sections describe the various classes of drugs. Not all of these agents have rigorous evidence for their utility beyond the inpatient phase. Nevertheless, the evidence supporting their use in the perioperative period is discussed, and when available, is followed by a discussion of literature supporting their utility in the discharge phase.

Acetaminophen and NSAIDs

Acetaminophen inhibits prostaglandin synthesis and is widely used to manage peri-operative pain, usually in combination with opioids. The low side-effect profile of acetaminophen has made it popular, especially in the elderly population that is more susceptible to drug side effects. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclo-oxygenase 1 and 2 enzymes for their analgesic and anti-inflammatory effects. NSAIDs are categorized into selective (COX-2 inhibitors, e.g., celecoxib, etoricoxib) and non-selective (ibuprofen, naproxen, diclofenac, ketorolac) agents based on their enzyme inhibition selectivity. Regarding medication regimen and dosing, no NSAID is superior, and all prescribed NSAIDs have a recommended range of doses for different purposes. At an equivalent dose, the analgesic effects of NSAIDs may show a ceiling effect, while the anti-inflammatory effects could still be increased. This means that once the maximal analgesic dose is reached, an additional increase in dose does not provide any further analgesic benefit [15]. For example, the analgesic ceiling dose for ibuprofen is 400 mg. An increase in dose to more than 400 mg does not provide any additional analgesic relief. Still, it does improve the anti-inflammatory effects of the medication until the maximum safe dose precludes any further increase [16].

An integral component of ERAS protocols, both acetaminophen and NSAIDs are used for pre-emptive and post-operative analgesia. NSAIDs are sometimes avoided in the perioperative period, especially for a prolonged duration due to their side effect profile. Gastrointestinal bleeding is a common side effect of NSAIDs, although this risk can be reduced by using selective COX-2 inhibitors such as celecoxib. Long-term use of NSAIDs may be associated with cardiovascular toxicity, especially in patients with atherosclerotic disease. Other concerns with the use of NSAIDs include anastomotic leakage after abdominal surgery, delayed fracture healing, postoperative bleeding, and risk of renal toxicity [17].

There is an abundance of literature supporting the efficacy of intravenous acetaminophen in lowering pain scores and the need for rescue analgesia in the immediate postoperative period [18, 19•, 20]. These findings have been corroborated by a recent meta-analysis of 6 RCTs that concluded that preemptive acetaminophen lowered opioid consumption in the first 24 h and pain scores for the first 12 h after surgery [21•]. However, as previously described, literature studying the analgesic efficacy of acetaminophen in the post-discharge phase is limited. A study by Desai et al. evaluated the utilization and efficacy of a multimodal analgesic regimen including opioids, acetaminophen, and NSAIDs at discharge. This study showed that while most patients were discharged with a multimodal regimen after common painful surgeries, a significant proportion of patients were discharged with opioids alone (around 24%). They concluded that combining acetaminophen with opioids was associated with decreased follow-up pain scores and readmissions. Further addition of NSAIDs was associated with further decreased follow-up pain scores and readmissions. Overall, patients receiving multimodal analgesia at discharge received 10%-40% fewer opioids per day compared to opioids only [22].

Another study compared the efficacy of preoperative acetaminophen with NSAIDs in patients undergoing outpatient ENT surgeries and assessed post-discharge pain scores. NSAIDs were most effective in reducing postoperative pain scores and analgesic requirements in the recovery room and post-discharge. In contrast, the analgesic efficacy of oral acetaminophen (2 g) was limited to the post-discharge period only [23].

NSAIDs alone are efficacious in reducing postoperative opioid requirements with rest and movement-related pain [24–27] and their consequent side effects [28]. However, the benefit of more prolonged administration of NSAIDs after discharge is limited. The American Association of Hip and Knee Surgeons, in their Clinical Practice Guidelines for the use of NSAIDs in total joint arthroplasty, recommended administration of oral selective NSAIDs for up to 6 weeks given the reduction of pain and opioid consumption after discharge [29•]. This recommendation was based on a single high-quality study that compared an oral selective COX-2 NSAID to placebo for six weeks and had overwhelming evidence favoring oral selective COX-2 NSAID use following primary total knee arthroplasty [30].

Gabapentinoids

Gabapentinoids are derivatives of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and block α2δ subunit-containing voltage-dependent calcium channels, leading to inhibition of cellular calcium influx and consequent attenuation of neurotransmission, making them efficacious in chronic neuropathic pain states [31]. Gabapentin and pregabalin are the two most used agents in this class and have been studied for their efficacy in reducing immediate perioperative pain and preventing chronic post-surgical pain.

Both single perioperative doses and longer post-discharge courses varying from 5–14 days have been trialed in various studies. Li and colleagues analyzed 14 RCTs of patients undergoing open hysterectomy and reported that gabapentin reduced total opioid consumption at 24 h postoperatively [32]. Another meta-analysis of RCTs assessing the efficacy of preoperative gabapentin in spine surgeries showed a reduction in pain scores and opioid consumption [33].

Like gabapentin, multiple studies have shown the efficacy of pregabalin in reducing immediate postoperative pain, especially when used pre-emptively, through its ability to reduce short-term central nervous system hypersensitivity via early reduction of neuronal excitability. This effect has been seen in various surgeries, including hysterectomy, thyroidectomy, septoplasty, discectomy, and knee arthroplasty [34–37]. Despite literature supporting the opioid-sparing effect of gabapentinoids in the immediate postoperative period, a recent meta-analysis on the subject concluded that gabapentinoids failed to show any clinically meaningful effect on post-operative acute, sub-acute or chronic pain. In contrast, the side effects such as sedation, gait imbalance and visual disturbances were significant [38••]. Moreover, when administered with other sedating agents such as opioids, there may be a higher risk of postoperative respiratory depression requiring noninvasive ventilation [39], leading to updated warnings by the FDA [40]. Given these side effects, with no noticeable effect on preventing chronic postoperative pain, the French Society of Anesthesia (FSA) and intensive care medicine recommended against routine use of these agents in outpatient surgery. However, other societies are yet to follow.

Data regarding the long-term use of gabapentinoids after discharge is limited to a handful of studies, some of which have explored a prolonged course of gabapentinoids for the prevention of chronic post-surgical pain. One of the largest RCTs studying the effect of extended use of pregabalin for up to 14 days postoperatively in knee arthroplasty patients reported a reduction in chronic neuropathic pain in the pregabalin group at three months and six months following surgery [41]. These authors used 300 mg of pregabalin preoperatively, followed by 150 mg twice daily (BID) for the first ten days, 75 mg BID on days 11 and 12, and 50 mg BID on days 13 and 14, post-operatively. The authors reported sedation, confusion, and dry mouth in the treatment group, especially on the day of surgery and on postoperative day one, and suggested that side effects could potentially be mitigated by using a smaller dose pre-operatively. In another double-blind RCT, hip arthroplasty patients were administered pregabalin at a dose of 75 mg BID while in house and for seven days after discharge. Compared to the placebo group, the pregabalin group consumed fewer opioids during hospitalization and had lower daily pain ratings and adjunct opioid use for one week following discharge [42]. On the other hand, a similar study on patients undergoing total knee arthroplasty concluded that compared to placebo, a two-week post-discharge course of pregabalin had no beneficial effects but increased sedation and decreased patient satisfaction [43]. The evidence is equally conflicting in the cardiothoracic surgery literature, where prolonged courses of gabapentinoids have been explored for their role in reducing chronic post-surgical pain. Anwar et al. compared usual care (scheduled paracetamol + morphine PCA) to a 14-day perioperative course of pregabalin alone to a 14-day course of pregabalin with 48 h infusion of ketamine postoperatively. The prevalence of pain was lower at 3 postoperative months for pregabalin alone (6% [3 of 50]) and in combination with ketamine (2% [1 of 50]) compared to the control group (34% [17 of 50]; odds ratio = 0.126 [0.022 to 0.5], P = 0.0008; and 0.041 [0.0009 to 0.28], P < 0.0001, respectively) and at 6 months for pregabalin alone (6% [3 of 50]) and in combination with ketamine 0% (0 of 5) compared to the control group (28% [14 of 50]; odds ratio = 0.167 [0.029 to 0.7], P = 0.006; and 0.000 [0 to 0.24], P < 0.0001) [44]. On the contrary, Brulotte et al. compared a five-day course of pregabalin to placebo in patients undergoing elective thoracotomy. They showed no difference in the incidence of chronic post-thoracotomy pain syndrome. However, the pregabalin group required significantly fewer analgesics, reported less moderate to severe average pain and presented significantly less neuropathic characteristics than patients in the placebo group 3 months after surgery [45].

A recent meta-analysis on the subject concluded that very little advancement had been made in the realm of pharmacotherapy to prevent chronic post-surgical pain [46••]. 5/17 meta-analyses for pregabalin and 0/4 for gabapentin proved superiority over placebo in preventing chronic postoperative pain. The literature in support of pregabalin in this role is most robust in total knee arthroplasty and cardiac surgery patients.

In addition, a recent RCT demonstrated a modest effect of perioperative gabapentin in promoting postoperative opioid cessation when continued for 72 h after surgery [47]. This RCT assessed the effect of perioperative gabapentin on remote postoperative time to pain resolution and opioid cessation and showed that although gabapentin did not affect the rate of pain resolution or the proportion of patients with chronic pain at six months or one year following surgery; it did promote opioid cessation and could therefore have a role in preventing chronic opioid use after surgery.

In summary, although immediate perioperative analgesic benefit with gabapentinoids has been brought into question, there is some evidence to support a post-discharge course varying from 5–14 days in select surgical subpopulations, those likely to develop chronic pain after heavy pro-nociceptive surgeries such as total knee arthroplasty and cardiac surgery for preventing chronic post-surgical pain. Clearly, more research is warranted in this realm. Risks and benefits need to be carefully

weighed when discharging patients on gabapentinoids, with detailed written instructions provided to identify side effects and for weaning off the drugs.

NMDA Antagonists:

Ketamine is an NMDA antagonist with intense analgesic efficacy that has received considerable interest as a perioperative analgesic adjunct, particularly for opioid-tolerant patients. While anesthetic doses of ketamine can cause hallucinations and dissociative side effects similar to PCP, in subanesthetic doses, the drug's NMDA antagonist properties improve perioperative analgesia. Low-dose ketamine infusions have been shown to have an opioid-sparing effect with a decrease in pain scores and opioid consumption in the immediate postoperative period. Most research on perioperative ketamine as an opioid-sparing adjunct has focused on the use of intravenous ketamine infusions, with these trials continuing an intraoperative infusion for up to 48 h postoperatively [48–51]. Doses are usually in the range of 0.1–0.2 mg/kg/hr. Psychosensory effects increase at doses above 0.3 mg/kg/hr, so this can be considered a soft upper limit [52].

Outpatient ketamine has been studied for chronic neuropathic pain states, including postherpetic neuralgia [53], complex regional pain syndrome (CRPS) [54], cancer pain [55, 56], orofacial pain [57] and phantom limb pain [58] in various small studies, most of which were descriptive in the form of case series and reports. Routes of administration include intravenous (IV), subcutaneous, oral, intranasal, and transdermal. Oral formulations of ketamine are not commercially available. The parenteral formulation is given as an oral solution or an extemporaneous preparation. The oral bioavailability of ketamine is low, reportedly 17% to 24% for oral racemic ketamine and 8% to 11% for oral S(+)-ketamine. After oral intake of ketamine, norketamine plasma concentrations are much higher than those of the parent drug [59]. Although the use of ketamine as an analgesic is now generally accepted, the evidence base for outpatient use remains poor. Moreover, safety data for outpatient oral use is lacking [60].

A recent pilot study studied oral ketamine for perioperative pain management in patients undergoing lower extremity amputation. Patients were administered a dose of 1.0 mg/kg oral ketamine an hour before surgery, followed 8 h later by a repeat dose and then 1 mg/kg dose three times daily on postoperative day 1. On the second postoperative day, this dose was reduced to 0.5 mg/kg three times per day. No serious and unexpected adverse events were reported, and pain scores ranged between 0.5–4. The authors concluded that oral ketamine was safe to use at this dose and convenient for the hospital floor and potential home use [61].

While extensive literature supports the opioid-sparing effect of ketamine in the immediate perioperative period, more research is required to explore the pharmacokinetics, safety, and efficacy of oral ketamine in the postoperative period, especially given its abuse potential, much like an opioid.

Antidepressants

Antidepressants are efficacious adjuncts in chronic neuropathic pain states. However, literature assessing their efficacy in the perioperative period is limited. The major groups of antidepressants include tricyclic antidepressants (TCAs) (e.g., amitriptyline, doxepin, imipramine), serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine, duloxetine), and selective serotonin–reuptake inhibitors (SSRIs) (e.g., paroxetine). There is very limited literature supporting the use of TCAs as a perioperative opioid-sparing adjunct. The untoward side effects such as sedation, anti-cholinergic side effects including dry mouth, blurry vision and urinary retention result in overall low compliance; this may also contribute to the fact that there do not appear to be any available studies evaluating the use of TCAs after discharge. SNRIs have some evidence supporting their utility in the perioperative period, with duloxetine and venlafaxine being the two most common drugs used in this class.

Duloxetine

Duloxetine is a SNRI that potentiates central serotonergic and noradrenergic pathways resulting in inhibition of nociceptive input via descending inhibitory pain pathways. Similar to other non-opioid analgesics, limited studies have evaluated duloxetine for its immediate postoperative benefits. Ho and colleagues, in their study on patients undergoing knee replacement surgery, reported reduced morphine requirements at 48-hour postoperatively, with 60 mg of duloxetine administered preoperatively and on day one post-operatively [62]. A similar RCT in patients undergoing abdominal hysterectomy showed significantly lower pain scores and opioid requirements at 24 hours with 60 mg of duloxetine administered preoperatively and at 24 hours postoperatively, with improved postoperative quality of recovery. These authors reported no side effects associated with the drug regimen, including nausea, vomiting, and recovery room discharge [63]. A recent meta-analysis evaluating the use of perioperative duloxetine questioned increased blood loss secondary to impaired platelet function and whether routine platelet function tests may be recommended if prolonged preoperative courses of SNRIs were administered [64]. However, the limited number of studies and patients involved precluded conclusions about the increased risk of bleeding or the need for routine testing of platelet function in patients receiving duloxetine for short periods in the perioperative period [64].

Zorrilla-Vaca et al. corroborated these results in a recent meta-analysis that showed duloxetine use to be associated with a significant reduction in pain scores and opioid use starting as early as four hours post-procedure [65]. There are very few studies evaluating the benefits of a longer course of duloxetine that would extend into the discharge phase. YaDeau et al. in their triple-blind RCT, compared a 15-day course of duloxetine to placebo in 106 patients undergoing knee arthroplasty. Duloxetine failed to improve pain with ambulation at the two-week mark, which was this study's primary outcome, although the authors did show a statistically significant reduction in opioid use and nausea postoperatively [66].

Duloxetine may be more beneficial in centrally sensitized patients, as shown by Ko et al. [67] in their study on patients undergoing total knee arthroplasty. Central sensitization was identified preoperatively with the use of the Central Sensitization Inventory (CSI). Forty patients randomized to the study group received 30 mg of duloxetine started one day prior to surgery and continued for six weeks after; these patients were compared to an equal number of controls. The duloxetine group had better performance across all the pain metrics and emotional and physical function in the 2-to 12-week postoperative period.

Venlafaxine

Venlafaxine is an SNRI with a chemical structure similar to tramadol, functioning as an analgesic with opioid activity [68]. Venlafaxine has shown efficacy in preventing post-mastectomy pain syndrome when continued in the post-discharge phase. In an RCT of 150 patients undergoing partial or radical mastectomy with axillary dissection, Venlafaxine ER 37.5 mg/d was compared to gabapentin 300 mg/d or placebo, administered for ten days starting on the night before the procedure. The gabapentin group showed reduced pain scores and morphine consumption in the acute phase but no improvement in chronic pain, except for a reduction in burning pain at six months post-operatively. On the contrary, venlafaxine had no analgesic effect immediately postoperatively. However, it showed a reduction in analgesic use from day two to twenty and a reduced incidence of post-mastectomy pain syndrome, and reduced analgesic use at six months [69]. In another RCT involving 15 patients with neuropathic pain after breast cancer treatment, the venlafaxine group showed significant improvement in pain when up titrated from a starting dose of 18.75 mg over a period of 10 weeks till the highest tolerable dose or maximum dose of 75 mg (37.5 mg BID) was reached. Interestingly, in this study, patients who were slow hydroxylizers (CYP2D6) with subsequent high venlafaxine serum concentrations had excellent pain control, emphasizing that higher doses may improve pain relief, provided the side effects were tolerated. There were no significant side effects in either group [70].

In summary, the perioperative use of antidepressants, such as duloxetine and venlafaxine, need to be explored further, not only for their opioid-sparing effects acutely but also for their potential to prevent chronic post-surgical pain; especially in surgeries such as mastectomies, thoracotomies, and orthopedic procedures that have a high risk of evolving into chronic pain. The most common side-effects associated with duloxetine are nausea, dry mouth, headache, constipation, dizziness, fatigue, insomnia, diarrhea, somnolence, and hyperhidrosis [71]. However, at doses used perioperatively, these side effects are rare.

Muscle Relaxants

Tizanidine

Tizanidine, an oral α2-agonist traditionally used for myofascial pain, neuropathic pain, back pain, and headaches, has recently entered the perioperative stage [72–75]. Systemic α_2-Agonists such as clonidine and dexmedetomidine have been studied extensively in the perioperative realm as adjuncts to anesthesia for their sedative, anxiolytic, sympatholytic, and analgesic effects [76]. Analgesia is thought to be mediated by central modulation of nociceptive transmission via both peripheral and supraspinal mechanisms [77]. There is plenty of literature in favor of perioperative clonidine and dexmedetomidine for their opioid-sparing effect, decrease in pain intensity, and nausea without prolonging recovery times. The impact of α2 agonists on chronic pain or hyperalgesia remains unclear [76]. Neither drug has been studied for post-discharge analgesia. Tizanidine is a commonly used outpatient muscle relaxant and was recently compared to placebo as a discharge adjunct in patients undergoing inguinal hernia repair. In this double-blind RCT involving 60 patients, tizanidine was started an hour before surgery and continued twice daily for the first postoperative week. Pain scores were significantly lower immediately postop, and especially so in the first seven days after surgery, the improved analgesia also resulted in an earlier return to normal daily activities. Analgesic related side effects (e.g., dry mouth, dizziness, drowsiness, headache, nausea, vomiting, dyspepsia or bleeding) were rare. The expected decrease in heart rate and blood pressure with tizanidine only occurred in the intraoperative phase in this study. The authors concluded that the central modulation of nociceptive transmission and the muscle relaxant effect of tizanidine might have improved analgesia [78]. Another double-blind RCT involving 70 patients undergoing laparoscopic cholecystectomy showed that preoperative oral tizanidine 90 min before the operation can reduce pain scores, analgesic consumption, analgesic-related side effects, and provide earlier return to normal daily activity. However, this study did not continue tizanidine in the post-discharge phase [79].

Cyclobenzaprine

Cyclobenzaprine, a commonly used outpatient muscle relaxant, is a centrally-acting agent that reduces tonic somatic motor activity by influencing alpha and gamma motor neurons at the level of the spinal cord [80]. There is a handful of studies that have used cyclobenzaprine as part of their multimodal analgesia (MMA) protocols for immediate postoperative pain control, but none have looked at this drug as a discharge adjunct. A comparative study of patients undergoing anterior cervical fusion showed that an MMA regimen including cyclobenzaprine, acetaminophen, pregabalin, and oxycodone resulted in lower overall narcotic consumption when compared to patient-controlled analgesia (PCA). This difference was associated with a shorter inpatient stay and a decrease in postoperative nausea/vomiting. Critically, MMA and PCA appeared to provide similar postoperative analgesia [81]. The Rush University Medical Center has developed their MMA protocol for spine surgeries to include cyclobenzaprine, a long-acting opioid, and an anticonvulsant prior to initiation of the general anesthetic. Cyclobenzaprine is continued on POD 0 and POD1 after surgery as part of a multimodal analgesia regimen [82]. On the other hand, an RCT in patients undergoing alloplastic breast reconstruction found no significant reduction in pain scores or the number of narcotic pills when cyclobenzaprine was used as an analgesic adjunct [83].

The side effects with cyclobenzaprine reported in literature are drowsiness, dry mouth, lethargy, tachycardia, agitation, hypertension and hypotension [84]. However, the incidence of adverse effects is dose-related and toxicity of cyclobenzaprine at doses lower than 1 g do not produce life-threatening cardiac, respiratory or neurological effects [85].

Diazepam

Diazepam (Valium) is a benzodiazepine often used as an anxiolytic but also used perioperatively given its muscle relaxation effect. Valium is often added to multimodal analgesic regimens in spine surgery [86], adolescent scoliosis repair [87], pectus excavatum repair [88] and thoracic outlet decompression surgery [89]. However, very few studies have explored discharging patients on valium as part of a multimodal analgesic regimen. In a retrospective study of thoracic outlet decompression surgeries, the adoption of a multimodal pain management regimen including scheduled ibuprofen and valium in the hospital reduced both the hospital length of stay and the mean in-hospital pain scores [89]. These authors mentioned transitioning the inpatient regimen of narcotics, ibuprofen, and valium to oral narcotics and valium at the time of discharge; however, the duration of valium use after discharge was not specified, neither were any pain outcomes measured after discharge. Another study added cyclobenzaprine preoperatively and valium immediately postoperatively for major spine surgery and showed improved pain scores before discharge from the recovery room and for the first postoperative day, but not beyond this time period [90]. Similarly, a feasibility trial performed in spine surgery patients compared a multimodal analgesic regimen including acetaminophen, valium, and gabapentin during hospitalization and at discharge to standard postoperative analgesia that relied primarily on narcotics. Patients in the former group had significantly lower pain scores and less opioid use on POD 0 and POD 1. This difference continued at two weeks post-discharge, although it did not reach the 0.05 significance level. These authors concluded that larger multicenter trials are needed to further examine the impact of multimodal analgesia on patient outcomes beyond pain and on postoperative opioid use [86].

In summary, there is limited evidence pointing to a beneficial effect of oral tizanidine and valium as an opioid-sparing adjunct at the time of discharge. Tizanidine could be considered in select surgeries that are often associated with muscle spasms. Notably, side effects have not been found to be significant. Larger prospective studies in varied surgical populations need to be performed to further explore the benefits of muscle relaxants, considering their reasonable side effect profile and potential for being continued in the outpatient setting.

Discussion

Opioids have been the mainstay of treatment for postoperative pain upon discharge, especially after relatively painful surgeries. However, this practice has an inherent risk of leading to persistent opioid use. Unfortunately, opioid prescriptions are not always utilized as directed and can potentially lead to diversion and substance abuse, contributing to the opioid epidemic: a global health care problem. Recent studies have explored the effect of reducing the number of opioid pills prescribed at the time of discharge on postoperative pain scores and refill requests. An ultra-restrictive opioid prescription approach was implemented in a study on gynecologic oncology surgical patients. This study showed a significant decrease in the number of opioids dispensed at discharge, without changes in postoperative pain scores, complications, or increases in the number of refill requests. Patients undergoing laparotomy and those needing more than five doses of opioids as an inpatient were sent home on three days' worth of opioids and were encouraged to use non-opioid medications, including Tylenol and NSAIDs, for seven days [91]. Howard et al. [92] similarly implemented an evidence-based prescribing guideline following laparoscopic cholecystectomy and reduced the prescription size by 63% without increasing the need for medication refills, thereby eliminating the excessive prescribing of roughly 7000 pills.

Although feasible and well-intentioned, in the absence of well-defined guidance for managing postoperative pain after discharge with non-opioids, these ultra-restrictive approaches risk undertreatment of pain. Moreover, this strategy may not work in certain patient subpopulations, such as those with chronic pain, opioid tolerance, or after more invasive and painful surgeries that are at risk for developing persistent post-surgical pain. Common elective surgical procedures often associated with chronic post-surgical pain include inguinal herniorrhaphy, breast surgery, orthopedic and cardiothoracic surgeries, with poorly controlled postoperative pain cited as one of the risk factors [93].

At present, there is a lack of studies focused on reducing the risk of persistent post-surgical pain and opioid use while managing acute postoperative pain adequately with opioid-sparing agents. There are several understudied non-opioid adjuncts that can be used for managing postoperative pain at discharge. If we are to limit opioid use after discharge, more research is urgently needed on managing postoperative pain with non-opioids.

Declarations

Ethical Approval The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

Conflicts of Interest No conflicts for any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
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•• Of major importance

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