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REVIEW ARTICLE

A Review of Adjunctive CNS Medications Used for the Treatment of Post-Surgical Pain

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Abstract Inadequate post-operative pain management can have significant impacts on patients' quality of life. Effective management of acute pain after surgery is important for early mobilization and discharge from hospital, patient satisfaction, and overall well-being. Utilizing multimodal analgesic strategies has become the mainstay of acute post-operative pain management. A comprehensive search was performed, assessing the published or otherwise publically available literature on different central nervous system (CNS) drugs [excluding opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen] and their uses to treat acute post-surgical pain. Included among the drugs evaluated in this review are anticonvulsants, *N*-methyl-D-aspartic acid (NMDA) agonists, local anesthetics, α_2-agonists, cannabinoids, serotonin–noradrenaline reuptake inhibitors (SNRIs), and serotonin–noradrenaline–dopamine reuptake inhibitors (SNDRIs). Timing, dosing, routes of administration, as well as mechanisms of action are discussed for these CNS drugs.

Key Points

Post-surgical pain is complex and involves physiological and psychological factors; central nervous system (CNS) medications can be useful adjuncts to treat acute pain within the perioperative setting.

By utilizing different classes of analgesic agents, the goals are to (1) provide superior pain relief at rest and with movement, (2) reduce opioid consumption and thereby the risk of misuse and (3) reduce adverse effects.

The adjunctive CNS medications chosen should be appropriately tailored to the patient, the surgery, and specific psychological co-morbidities.

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1 Introduction

Pain is one of the leading causes of disability and significantly impacts patients' quality of life. After surgery, patients are encouraged to resume mobilization as soon as possible in order to facilitate recovery, reduce the likelihood of complications and reduce hospital length of stay and costs associated with hospitalization and extent of caregiver requirements post-discharge [1]. Moderate-to-severe, acute post-operative pain is a major factor that delays functional recovery [2]. Effective management of acute post-operative pain after surgery is important for early mobilization, discharge from the hospital, patient satisfaction, and overall functioning and well-being [3]. Post-operative pain should be managed early and aggressively, in part because severe post-operative acute pain is a risk factor for the development of chronic post-surgical pain (CPSP) [4, 5].

Standard perioperative analgesics include acetaminophen/paracetamol, non-steroidal anti-inflammatories [non-steroidal anti-inflammatory drugs (NSAIDs)], and opioids. Their uses are limited by several factors, including dose-related systemic toxicities causing hepatic and renal dysfunctions, and opioid-induced ventilatory impairment, respectively. Although the effect of NSAIDs on renal function is fairly benign in a short course, surgeons are often hesitant to allow the use of these drugs, because of procedure-specific concerns (i.e., anastomotic leaks [6], spinal fusions [7]). Furthermore, NSAIDs are often contraindicated to most procedures in certain surgical specialties (i.e., vascular surgery, neurosurgery).

Forays into adjunctive analgesic medications through the utilization of multimodal analgesic strategies have become central in acute post-operative pain management [8, 9]. Several different receptors, channels, and signaling molecules have been identified to be involved in analgesic mechanisms, and we seek to explore their effects in this article. Given the multiple pathways through which nociceptive activity reaches the central nervous system (CNS), different classes of analgesic agents with different routes of administration are used to (1) provide superior pain relief at rest and with movement, (2) reduce opioid consumption and misuse, and (3) reduce adverse effects. Pharmacological agents used to treat acute post-operative pain come from diverse drug classes; many are used off-label, having been repurposed for pain management, for which their efficacy and use were not initially intended. This article critically reviews CNS medications that are now used for the treatment of post-surgical pain.

2 Methods

A comprehensive review assessing the published or otherwise publically available literature for different CNS drugs and their uses to treat post-surgical pain was performed. Our purpose was to specifically examine medications that have been repurposed for post-operative analgesia. As such, a decision was made to exclude standard analgesics including acetaminophen/paracetamol, non-steroidal anti-inflammatories, and opioids. Furthermore, these standard analgesics have been extensively studied. The drugs included in the current search are as follows: (1) anticonvulsants (gabapentin, pregabalin, and lamotrigine), (2) *N*-methyl-D-aspartic acid (NMDA) antagonists (ketamine, amantadine, and magnesium), (3) α_2-agonists (dexmedetomidine and clonidine), (4) local anesthetics (lidocaine), (5) cannabinoids, (6) serotonin–noradrenaline reuptake inhibitors [SNRIs] (venlafaxine and duloxetine), and (7) serotonin–noradrenaline–dopamine reuptake inhibitor [SNDRIs] (nefopam).

We evaluated the efficacy of the CNS medications to reduce acute pain. Our secondary outcomes were opioid consumption, time to first analgesic request, efficacy of combination analgesic therapies, and adverse effects.

A comprehensive search strategy was developed to identify all articles that evaluated the drugs mentioned above. The following databases were searched: Ovid Medline, Ovid Medline In-Process, Embase, and International Pharmaceutical Abstracts. Controlled vocabulary terms, text words, and keywords were used in the search strategies (see the Appendix, provided in the electronic supplementary material). Databases were searched from January 2000 to June 22, 2016 using individualized search strategies for each database. Informal searches using Google Scholar and PubMed were performed to obtain any additional articles.

Inclusion criteria for the studies were (1) enrolled patients aged $\geq$18 years old, (2) one of the drugs mentioned above were administered, and (3) the drug was compared with either a placebo or a control. We limited articles to systematic reviews, meta-analyses, and randomized controlled trials (RCTs). Ketamine, gabapentin, pregabalin, lidocaine, dexmedetomidine, and clonidine have all been well studied; therefore, we limited our search for these drugs to systematic reviews and meta-analyses (SR-MAs). For the other drugs, we searched for RCTs and SR-MAs. All articles included evaluated pain scores in the acute setting, using a valid and reliable measure of pain. Exclusion criteria were (1) animal studies, (2) studies on subjects <18 years old, (3) case reports, (4) case series, (5) cohort studies, (6) commentaries, and (7) letters to the editor.

Two independent reviewers (AR and HM) screened the titles and abstracts using the inclusion and exclusion criteria outlined above. We elected to only include the most recent or relevant articles for each of the drugs. For the SR-MAs, we identified primary studies included to further evaluate the data.

Publications included in this review were assessed for quality using standardized and validated tools. RCTs were quality assessed using the modified Jadad scale and SR-MAs using A Measurement Tool to Assess Systematic Reviews (AMSTAR).

3 Results

3.1 Quality Assessment

A total of 531 publications were identified in our search. A secondary supplemental search included five publications that met our inclusion criteria. A total of 13 SR-MAs and nine RCTs were included in this review. AMSTAR evaluation (Table 1) of the SR-MAs scored six publications with 9/11, five with 8/11, one with 7/11 and one with 4/11, suggesting six were high quality and seven were moderate quality. Modified Jadad scale evaluation of RCTs (Table 2) scored four publications with 8/8, three with 7/8, one with 6/8, and one with 5/8. Chang et al. reported that they assessed the quality of the studies included in their review; however, they did not make any mention of the results or provide access to them [10]. The study by Elia et al. scored 4/11 because we were unable to access the supplementary material that assesses the scientific quality of the studies that were included in this review [11].

3.2 Anticonvulsants

3.2.1 Gabapentin

Gabapentin is an inhibitor of the $\alpha_2\delta$-1 subunit of the Ca^{2+} voltage-activated channels, leading to reduction in post-synaptic excitability [12]. This is believed to modulate release of excitatory neurotransmitters, possibly inhibiting pain transmission and central sensitization [12].

Four recent systematic reviews were included to evaluate gabapentin as an analgesic medication for post-operative pain. One meta-analysis focused on total knee arthroplasty, with patients receiving between 400 and 600 mg of gabapentin pre-operatively [13], while another covered several surgical subtypes, with patients receiving between 300 and 1600 mg of gabapentin pre-operatively [14].

Two systematic reviews found that patients receiving gabapentin reported lower acute pain scores compared with patients receiving placebo [13, 14], with a mean difference of -2.67 on the visual analog scale (VAS) scale, $p = 0.024$ [13]. The gabapentin group also consumed fewer opioids in the first 48 h post-operatively [13, 14], with one review reporting a mean difference of -7.29 mg of morphine, $p = 0.004$ [13]. One of the RCTs from the Dauri et al. [14] systematic review found that the addition of rofecoxib 50 mg to gabapentin 1200 mg led to a shorter duration of opioids when compared with placebo, which was not seen with either drug alone in patients who received abdominal hysterectomies [15].

3.2.2 Pregabalin

Pregabalin also inhibits the $\alpha_2\delta$-1 subunit of the Ca^{2+} voltage-activated channels, leading to reduction in post-synaptic excitability [12]. Unlike gabapentin, pregabalin has greater bioavailability due to an amino acid substitution that enables improved absorption via the small intestine [12].

Three recent SR-MAs have evaluated pregabalin for pain relief following surgery. One of the systematic reviews included patients undergoing several different surgeries who received between 50 and 300 mg of pregabalin before surgery [16], while another included patients undergoing several different surgeries receiving between 75 and 300 mg [17]. Two of the systematic reviews reported a significant decrease in acute pain scores 24 h following surgery for the pregabalin group compared with placebo [16, 17]. Pain scores at rest were only reduced at doses >100 mg and doses >300 mg with movement [17]. Eipe et al. grouped surgeries into model 1 [surgeries associated with a pronociceptive mechanism (spine, joint arthroplasty, and amputations, etc.)] and model 2 [surgeries not associated with a pronociceptive mechanism (abdominal laparoscopic surgery, gynecological procedures, etc.)] [18]. Model 1 reported significantly lower pain scores at rest, with a mean difference [95% confidence interval (CI)] of -1.09 (-1.80 to -0.37), $p = 0.003$, and with movement, with a mean difference (95% CI) of -0.94 (-1.23 to -0.65), $p < 0.00001$) [18]. However, for model 2 there was no significant difference between pain scores for the pregabalin and placebo groups [18]. Two systematic reviews have reported a statistically significant reduction in opioid consumption in the first 24 h with pregabalin use [16, 17]. There was no statistical difference in opioid consumption between patients receiving ≤75, 150–300, and ≥300 mg dose levels of pregabalin [17].

3.3 *N*-Methyl-D-Aspartic Acid (NMDA) Antagonists

3.3.1 Ketamine

Ketamine is a noncompetitive NMDA receptor antagonist that has been shown to attenuate spinal NMDA-mediated sensitization of dorsal horn neurons [19].

Table 1 Assessment of multiple systematic reviews (AMSTAR) ratings

References	Drug	Was an 'a priori' design provided?	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Was a list of studies (included and excluded) provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies assessed and documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	Was the likelihood of publication bias assessed?	Was the conflict of interest included?	Score
Dauri et al. [14]	Gabapentin	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	8
Zhai et al. [13]	Gabapentin	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Lam et al. [16]	Pregabalin	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Eipe et al. [18]	Pregabalin	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Mishriky et al. [17]	Pregabalin	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Wang et al. [21]	Ketamine	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Laskowski et al. [20]	Ketamine	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	8
De Oliveira et al. [2]	Magnesium	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	9
Elia et al. [11]	Clonidine	Y	N	Y	Y	N	Y	N[a]	Cannot answer[c]	Y	N	N	4
Engelman et al. [34]	Clonidine	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	8
Schnabel et al. [38]	Dexmedetomidine	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	8
Chang et al. [10]	Lidocaine	Y	Y	Y	Y	N	Y	N[b]	Cannot answer[c]	Y	Y	N	7
Vigneault et al. [32]	Lidocaine	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	8

AMSTAR A Measurement Tool to Assess Systematic Reviews

[a] Was unable to access

[b] Stated that they did it, but no table or reference to table was made

[c] Cannot answer question 8, if answered no to question 7

Table 2 Modified Jadad ratings of RCT quality

References	Drug	Is this a RCT study?	Reported as randomized	Randomization is appropriate	Double blinding is reported	Double blinding is appropriate	Withdrawals are reported by number and reason per arm	Method(s) used to assess adverse events is described	Method(s) of statistical analysis is described	Inclusion and/or exclusion of the requirements is reported	Score
Bujak-Gizycka et al. [26]	Amantadine	Y	Y	Y	Y	Y	Y	Y	Y	Y	8
Gottschalk et al. [25]	Amantadine	Y	Y	Y	Y	Y	Y	Y	Y	Y	8
Snijdelaar et al. [27]	Amantadine	Y	Y	Y	Y	Y	Y	Y	Y	Y	8
Yazdani et al. [24]	Amantadine	Y	Y	Y	Y	Y	N	N	Y	Y	6
Ho et al. [48]	SNRI	Y	Y	Y	Y	Y	Y	N	Y	Y	7
Amr et al. [49]	SNRI	Y	Y	N	Y	Y	N/A	N	Y	Y	5
Beaulieu et al. [40]	Cannabinoid	Y	Y	Y	Y	Y	Y	Y	Y	Y	8
Buggy et al. [41]	Cannabinoid	Y	Y	N	Y	Y	Y	Y	Y	Y	7
Na et al. [44]	SNDRI	Y	Y	Y	Y	Y	Y	N	Y	Y	7

RCT randomized controlled trial, *SNDRI* serotonin−noradrenaline–dopamine reuptake inhibitor, *SNRI* serotonin–noradrenaline reuptake inhibitor

Two systematic reviews evaluating ketamine as a post-operative analgesic medication were included. One of the reviews included 70 studies that covered numerous surgeries [20]. 37.5% of the studies found a significant decrease in early pain scores (30 min—4 h) and 25% of the studies showed a significant decrease in pain scores between 24 and 72 h [20]. The other systematic review evaluated the addition of ketamine to a patient-controlled analgesia (PCA) pump. Patients undergoing a variety of surgeries who received ketamine reported a statistically significant reduction in VAS pain scores at rest and with movement at all time points up until 72 h compared with placebo [21].

With the addition of ketamine to the PCA, patients consumed less morphine in the first 24 h post-operatively compared with those who did not receive ketamine [21]. Laskowski et al. also performed a meta-analysis on 64 studies, they found that patients who received ketamine had a statistically significant reduction in opioid consumption compared with controls [20]. Subgroup analysis demonstrated the largest difference in opioid consumption for upper abdominal and thoracic procedures, followed by orthopedic, intra-abdominal, and lower abdominal surgeries [20]. The least reduction in opioid consumption was seen in those undergoing head and neck surgery, dental surgery, and tonsillectomy [20]. Ketamine was also found to be effective at increasing the time to first post-operative analgesia when compared with placebo [20]. There have not been dedicated dose-finding studies performed for intra-operative ketamine. However, a Cochrane review indicated there does not appear to be a further significant morphine-sparing effect beyond 30 mg/24 h [22].

3.3.2 Amantadine

Amantadine is a noncompetitive NMDA receptor antagonist that reduces neuronal excitability within the dorsal horn of the spinal cord [23, 24]. Four RCTs evaluating the use of amantadine were included in our study. The study populations of the RCTs were open reduction and internal fixation of mandibular unilateral body fracture receiving 100 mg of amantadine [24], abdominal hysterectomy receiving 200 mg of amantadine [25], idiopathic scoliosis receiving either 50 or 100 mg of amantadine depending on the patient's weight [26], and radical prostatectomy receiving two doses of 200 mg pre-operatively followed by three doses of 100 mg post-operatively [27]. One of the RCTs reported lower pain scores for the first 6 h post-operatively [26], while another only reported lower pain score for the first hour [27]. However, one of the RCTs reported lower pain score for the control group at the time of extubation, but at no time point after that [25], and the final RCT reported no difference between the two groups [24]. Two of these studies also reported that the amantadine group consumed less opioid for the first 48 h [26, 27]. The group that received multiple doses of amantadine had a 32% reduction in morphine consumption over the first 48 h after surgery, in comparison with placebo [27].

3.3.3 Magnesium

Magnesium functions as an antagonist to the NMDA receptor [28]. A recent systematic review and meta-analysis in which patients received magnesium either as a 50 mg/kg bolus, 30–50 mg/kg infusion, or 30–50 mg/kg bolus followed by an 8–25 mg/kg/h infusion evaluated the ability of magnesium to reduce post-surgical pain [2]. Perioperative intravenous (IV) magnesium was successful in reducing pain at rest and at 4 and 24 h, as well as pain with movement at 24 h post-operatively when compared with placebo [2]. Opioid consumption was also lower in the magnesium group by a mean difference of −10.52 mg (95% CI −13.5 to −7.54) morphine equivalents [2].

3.4 Local Anesthetics

3.4.1 Lidocaine

Lidocaine exhibits its effect on the CNS via direct sodium channel blockade. When neuraxial anesthetic techniques are utilized, a sensory and motor blockade is often present. Lidocaine also interacts with other factors involved with nociceptive transmission—muscarinic agonists, glycine inhibitors, release of endogenous opioids, and the reduced production of excitatory amino acids, neurokinins, and thromboxane A2 [29]. Lidocaine has been shown to have analgesic [29], anti-hyperalgesic [30], and anti-inflammatory properties [29, 31]. We examined the literature regarding IV lidocaine infusions.

There were conflicting results regarding the efficacy of lidocaine infusions for the treatment of acute post-operative pain. One meta-analysis, in which patients received a 1–6 mg/kg bolus followed by 1–3 mg/kg infusions (one included study has infusions up to 21 mg/kg), found significantly lower VAS pain score at rest in patients treated with lidocaine at 6 and 12 h, but not at 24, 48, or 72 h [32]. However, another meta-analysis, in which patients received 0.5 mg/kg bolus followed by a 1.5–2 mg/kg/h infusion throughout the surgery, reported that there was no significant difference at any time point between 2 h and 3 days. Both of these studies showed that the lidocaine infusion group consumed less morphine than the placebo group [10, 32].

3.5 α_2-Agonists

3.5.1 Clonidine

Clonidine is another α_2-adrenoreceptor agonist that has anti-nociceptive activity via peripheral, supraspinal, and primarily spinal cord mechanisms such as activation of descending noradrenergic pathways [33]. Clonidine has been shown to prolong the duration of analgesia [11].

Two recent systematic reviews evaluated clonidine as an analgesic drug. Both included studies in which patients underwent different surgeries and received intrathecal clonidine [11, 34]. These reviews reported that patients who received clonidine had a statistically significant increase in the time to first analgesia request compared with the placebo group [11, 34]. One study also demonstrated that patients receinving clonidine used less morphine compared to those receiving placebo medication [34]. Subgroup analysis found that only those who received 90–150 mcg of clonidine had a statistically significant reduction in morphine use; this effect was not seen at lower doses [34]. Overall, α_2-adrenoreceptor agonists (clonidine and dexmedetomidine) when evaluated as a class demonstrated a reduction in pain scores for the first 2 h post-operatively [35].

3.5.2 Dexmedetomidine

Dexmedetomidine is a selective α_2-adrenoreceptor agonist that has anti-nociceptive activity via peripheral, supraspinal, and primarily spinal cord mechanisms such as activation of descending noradrenergic pathways [33]. Dexmedetomidine has eight times more α_2 specificity than clonidine [36]. Dexmedetomidine has also been shown to inhibit activation of microglia in the spinal dorsal horn after nerve injury, reduce perioperative catecholamine release, and decrease the demand of intraoperative anesthetics [37].

A recent systematic review reported patients who received dexmedetomidine had statistically lower pain scores at all time points up to 48 h compared with placebo following major surgery [38]. There was a greater mean difference in post-operative pain scores when dexmedetomidine was administered first as a bolus then followed by a continuous infusion compared with bolus or continuous infusion alone [38]. The patients in the dexmedetomidine group consumed less morphine compared with the placebo group at 2, 24, and 48 h post-operatively [38]. A meta-analysis demonstrated the addition of clonidine or dexmedetomidine resulted in superior pain score and decreased morphine consumption [35]. However, no direct comparison between the two alpha agonist agents was performed.

3.6 Cannabinoids

Agonistic activity at cannabinoid receptors causes inhibition of release of neurotransmitters including glutamate, GABA, noradrenaline, dopamine, serotonin, and acetylcholine. Alterations in signaling modulates nociceptive thresholds at peripheral, spinal, and supraspinal levels [39].

There have been limited studies involving cannabinoids and post-surgical pain. A multi-dose (1 and 2 mg) nabilone trial for predominantly gynecological and orthopedic surgeries was administered as an adjunct to opioid treatment. The 2-mg nabilone dose was paradoxically associated with increased pain at rest and with movement [40]. Another study examined oral delta-9-tetrahydrocannabinol (delta-9-THC) post-operatively for open abdominal hysterectomy. Patients were given a single 5-mg dose or placebo after discontinuation of IV PCA on postoperative day (POD) 2. There were no differences in summed pain intensity at 6 h or time to request for rescue analgesia [41].

3.7 Serotonin–Noradrenaline–Dopamine Reuptake Inhibitors (SNDRIs)

Nefopam is an SNDRI, and its mechanism of action for analgesia is related to the reuptake inhibition effects on serotonin, noradrenaline, and dopamine. It also has a role in modulating the development of hyperalgesia through interactions with calcium and sodium channels in the glutamatergic pathway, which cause decreased activation of NMDA receptors [42].

Nefopam has been studied in combination with opioids, non-steroidal anti-inflammatories (NSAIDs), and acetaminophen as a pre-, intra-, and post-operative analgesic [43]. A recent review on nefopam demonstrated significant reduction in morphine consumption in the range of 20–40% in patients with moderate to severe pain following abdominal and orthopedic surgeries. Trials involving combinations of nefopam with NSAIDs and acetaminophen have also demonstrated strong synergy in analgesic effects [43].

A recent RCT compared pre-operative nefopam (20 mg) to placebo administration in breast cancer surgery [44]. The nefopam group provided superior pain scores at multiple time points up to 24 h, along with reduced rescue analgesic drug administration. Compared with traditional analgesics, nefopam does not confer the risks of platelet dysfunction (NSAIDs), nor does it cause respiratory depression (opioids) [43]. Furthermore, combining nefopam with opioid and non-opioid analgesics has demonstrated opioid-sparring and analgesic synergy effects, respectively [43]. In addition to being used as a combination drug, nefopam has intrinsic analgesic effects that are comparable to IV PCA fentanyl

post cardiac surgery [45]. Nefopam could potentially be integrated within multimodal analgesic pathways in countries within which it has been approved for patient use.

3.8 Serotonin–Noradrenaline Reuptake Inhibitors (SNRIs)

SNRIs have demonstrated efficacy in the treatment of chronic neuropathic pain [46]. Serotonin and noradrenaline have been postulated to be involved in modulating the descending inhibitory pain pathways [47].

Two trials involving venlafaxine and duloxetine were performed in the acute perioperative setting [48, 49]. Patients undergoing mastectomy were given venlafaxine (37.5 mg), gabapentin (300 mg), or placebo for 10 days starting 1 day pre-operatively [49]. Venlafaxine patients required less analgesia in the form of codeine and acetaminophen from POD 2–10 and experienced reduced pain with movement from POD 8–10. An RCT that examined duloxetine therapy in patients who underwent knee replacement receiving a 60-mg dose 2 h pre-operatively and on POD 1 demonstrated decreased morphine consumption 48 h post-operatively, but no difference in pain scores [48].

4 Discussion

4.1 Acute Post-Operative Pain

Acute post-surgical pain occurs because of tissue trauma, and typically a greater degree of tissue trauma is associated with more severe pain [50]. Direct tissue trauma leads to activation of thermal and mechanoreceptors, while chemoreceptors are activated through the release of local mediators including reactive oxygen species, kinins, prostanoids, adenosine triphosphate (ATP), histamine, and substance P [51, 52]. Signal transduction is mediated via receptors on Aδ and C afferent fibers and conducted to the CNS; nociceptor sensitization serves to magnify the signal. Acute pain is reflective of several mechanisms which include nociceptive transduction and transmission, sensitization of peripheral somatic and visceral nerves and central neurons, and loss of local and descending inhibition in the brainstem and spinal cord [53].

The mainstay of post-operative pain management has been the administration of opioids [54]. While opioids are effective for the management of moderate to severe acute pain, opioid administration is also associated with sedation, nausea, vomiting, pruritus, ileus, urinary retention, constipation, and respiratory depression [54]. Multimodal opioid-sparing analgesia has become increasingly popular over the last decade as a way of treating pain and preventing the side effects of opioids [55]. The most common non-opioid analgesics used in the perioperative setting include lidocaine, acetaminophen, NSAIDs, ketamine, gabapentin, pregabalin, clonidine, and dexmedetomidine, which are all medications that exert CNS effects [54, 55]. These medications can be utilized as needed in the appropriate patient undergoing a surgical procedure that induces significant injury and is associated with severe pain. Patients with neuropathic descriptors of their pain immediately post-operatively are at increased risk for the development of persistent pain, and the addition of these adjuncts may be helpful in this setting.

4.2 Perioperative Timing of Analgesic Administration

The timing of the administration of centrally acting medications for post-operative pain has been debated for years. Based on the evidence, pre-operative anticonvulsant medications have demonstrated efficacy with respect to opioid and pain reduction following surgery when given pre-operatively [56]. This is best achieved through administration of the medication in the pre-operative holding area approximately 2 h prior to surgery to allow adequate time for drug absorption before the surgical incision. Evidence is lacking with respect to the use of SNRIs in the acute post-operative setting. Based on early studies, the use of nefopam may confer additional benefit for post-operative analgesia [44].

Common drugs used intra-operatively include NMDA antagonists, local anesthetics, and α_2-agonists. Ketamine and magnesium are commonly given as boluses and infusions intra-operatively prior to skin incision to obtain the best post-operative analgesic effect. Administration of a benzodiazepine prior to ketamine is thought to minimize unwanted hallucinations and nightmares, which occasionally occur with its use [57].

The best evidence for lidocaine infusions is for patients undergoing abdominal surgery, and the drug should be continued for 1 h post-operatively [32]. Dexmedetomidine confers anxiolytic, analgesic, and sedative effects, and is a versatile drug in providing procedural sedation. An initial loading dose (1 mcg/kg over 10 min) followed by an infusion (0.2–0.7 mcg/kg/h) provides the fastest onset to optimal surgical conditions and also demonstrates good post-operative analgesia [38].

Post-operative pain management is challenging in that the patient is not always monitored one to one by an anesthesiologist or a member of the anesthetic care team. In the post-anesthetic care unit (PACU), the most commonly used medications include lidocaine and ketamine. Lidocaine infusions may be a continuation of what was initiated in the operating room (OR). Ketamine is generally discontinued >30 min prior to the end of the case to avoid

psychotropic effects on awakening. In patients with difficult to treat pain that is refractory to standard regimen of opioids, ketamine can be given as a bolus or an infusion on the wards post-operatively.

Pre-operative chronic pain medications should be continued throughout the perioperative time period if possible. These medications include anticonvulsants, cannabinoids, SNRIs, and tricyclic antidepressants (TCAs). A systematic review by Ho et al. concluded continuation of anticonvulsants reduced pain scores and lowered opioid requirements post-operatively [58]. Although there is no evidence, cannabinoids (i.e., nabilone) can be initiated for patients who took medical cannabis for chronic pain pre-operatively as a means to replace the THC and/or cannabidiol (CBD) content.

4.3 Consideration for CNS Drugs Used in the Perioperative Setting

The pillars of post-operative pain management revolve around multimodal analgesia using standard acetaminophen/paracetamol, NSAIDs, and opioids [59]. Various techniques (i.e., regional anesthesia) exist, if feasible, for providing patients superior analgesia compared with systemic analgesic therapy, but these are beyond the scope of this review. Medications highlighted in this review are not commonly used for analgesia, and as such it is difficult to formulate a definitive recommendation for their use in the perioperative setting. However, the existence of analgesic properties in these medications allows their use as adjunct analgesics in our armamentarium. Medications highlighted in this review should be considered when treating patients who have complex and/or chronic pain and have analgesic requirements beyond safe and effective doses of our standard analgesics. These medications should be used with caution as their adverse effects may synergize with adverse effects of our standard analgesics.

5 Limitations

This review is limited by the subset of studies that were identified and included; given we limited our search to the time period 2000–2016, important articles prior to 2000 may have been excluded. Several systematic reviews and meta-analysis were available for gabapentin, pregabalin, ketamine, lidocaine, and clonidine. A limited number of RCTs existed for memantine, cannabinoids, and SNRIs; therefore recommendations on their use in the perioperative setting are limited and more research needs to be conducted. The SR-MAs included heterogeneous patient populations, different surgical procedures, and variability in drug administration (i.e., timing, route, dose, and duration), which limits generalized recommendations. The purpose of this review was to examine CNS medications that are utilized for the treatment of acute post-surgical pain. Finally, these CNS medications likely play a greater role in the treatment of neuropathic pain, rather than inflammatory and nociceptive pain, and are likely best utilized in patients either presenting with a prior chronic pain condition or those patients describing new neuropathic pain features (i.e., stabbing, shooting, electric shock-like symptoms) within the immediate post-operative period that does not improve over the next 72 h.

6 Conclusion

Many medications find themselves repurposed for conditions outside of the scope for which they were intended. Because post-surgical pain is complex and involves physiological and psychological factors, CNS medications are useful adjuncts within the perioperative setting. The medications utilized should be appropriately tailored to the patient, the surgery, and specific psychological co-morbidities. Furthermore, the risks and benefits of each CNS drug utilized should be considered. Dosing, administration route, frequency, duration, and timing of drug administration need to be considered for each case. Ideally, the goal of providing adequate analgesia in the post-operative setting is to reduce patient suffering and improve functional outcomes after major surgery by returning patients to pre-operative functioning as soon as possible. Early identification of patients with neuropathic pain features and implementation of CNS medications are a possible path forward to enable improved pain outcomes and reduce persistent opioid use after surgery. Finally, to optimize patient outcomes, clinical services (such as transitional pain services) are needed, which identify patients at risk preoperatively, perioperatively, and postoperatively for going on to develop persistent postoperative pain. Transitional pain services will provide care into the post-discharge period, and provide education immediately for patients suffering with persistent pain, early pharmacological intervention, psychoeducation, and targeted mental and physical health interventions [60]. The utilization of pharmacological and non-pharmacological strategies aims to reduce CNS hyperexcitability with the goal of reducing pain and facilitating function both in the short and long term following major surgery.

Compliance with Ethical Standards

Conflict of interest Ajit Rai, Howard Meng, Aliza Weinrib, Marina Englesakis, Dinesh Kumbhare, Liza Grosman-Rimon, Joel Katz, and Hance Clarke have no financial interests or conflicts of interest to declare.

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