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CLINICAL PRACTICE

Multimodal therapies for postoperative nausea and vomiting, and pain

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Editor's key points

- Postoperative nausea and vomiting along with pain are among the major perioperative concerns of most surgical patients and their anaesthetists.
- Multimodal approaches to both PONV and pain have been shown to improve treatment efficacy and reduce side-effects for high-risk patients undergoing surgical procedures.
- These approaches integrate both pharmacological and non-pharmacological interventions made before operation, intraoperatively, and after operation.

Summary. Postoperative nausea and vomiting (PONV) and pain are two of the major concerns for patients presenting for surgery. The causes of PONV are multifactorial and can largely be categorized as patient risk factors, anaesthetic technique, and surgical procedure. Antiemetics work on several different receptor sites to prevent or treat PONV. This is probably why numerous studies have now demonstrated that using more than one antiemetic is usually more effective and results in fewer side-effects than simply increasing the dose of a single antiemetic. A multimodal approach to PONV should not be limited to drug therapy alone but should involve a holistic approach starting before operation and continuing intraoperatively with risk reduction strategies to which are added prophylactic antiemetics according to the assessed patient risk for PONV. With the increasing understanding of the pathophysiology of acute pain, especially the occurrence of peripheral and central hypersensitization, it is unlikely that a single drug or intervention is sufficiently broad in its action to be adequately effective, especially with moderate or greater pain. Although morphine and its congeners are usually the foundation of pain management regimens, as their dose increases so does the incidence of side-effects. Thus, the approach for the management of acute postoperative pain is to use multiple drugs or modalities (e.g. regional anaesthesia) to maximize pain relief and reduce side-effects.

Keywords: nausea, postoperative; pain, postoperative; vomiting, postoperative

Postoperative nausea and vomiting

While multiple advances have been made in the last several years in minimizing adverse outcomes after anaesthesia, patients continue to rank nausea/vomiting as their most undesirable surgical outcome.[1 2] While the incidence of postoperative nausea and vomiting (PONV) varies considerably in both the inpatient and outpatient setting,[3–6] studies indicate that the incidence of nausea ranges from 22% to 38%[7] and the incidence of vomiting ranges from 12% to 26%.[7] Multiple risk factors have been identified that increase the incidence of PONV. The incidence of PONV in high-risk patients is much higher (60–70%).[8] The administration of antiemetic drugs reduces this incidence, especially the judicious use of multiple antiemetics.[9] Post-discharge nausea and vomiting (PDNV) defined from 24 h post-discharge up to 72 h has an incidence of up to 55%.[5 10–12] It appears that the risk factors for PDNV are different from those for PONV.[13]

The multimodal approach of using more than one antiemetic was initially conceived and described due to the limited effects of single-drug therapy[14] and the finding that multiple drug therapies resulted in a lower incidence of PONV.[15] While numerous trials have validated the utility of this methodology, it should be understood that the multimodal approach extends far beyond intraoperative pharmacotherapy and starts with non-pharmacological interventions in the preoperative area.[16]

Identification of risk factors for PONV

Several factors such as female gender and history of PONV/motion sickness were identified retrospectively as early as 1960[17] as risk factors for PONV. In 1993, a study was performed using logistic regression analysis to prospectively look at factors for PONV in a small cohort of patients.[18] Subsequently, Apfel and colleagues[8] identified four risk factors that form the basis for the Apfel scoring system: female gender, history of PONV/motion sickness, non-smoking status, and use of postoperative opioids. Each risk factor increases the likelihood of PONV by ~18–22%.[8] Identification of baseline risk using the Apfel criteria is important, since an increase in risk

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factors increases the number of subsequent therapies required.[9]

Although Apfel defined the risk criteria with the largest impact on PONV, multiple other risk factors have been identified. These can be broadly divided into three categories: patient risk factors, anaesthetic technique, and surgical procedure. Patient risk factors include female gender from puberty, non-smoking status, previous history of PONV/motion sickness, and genetic predisposition.[3 19–22] Anaesthetic technique includes the use of inhalation agents, nitrous oxide, large-dose neostigmine, and intraoperative and postoperative opioid use.[9 19 23–28] Surgical factors include longer duration of surgery and different types of surgeries.[8 20 22 29] However, whether longer surgeries are directly causal is difficult to prove, since higher doses of opioids and longer exposure to inhalation anaesthetics (MAC-hours) are likely to occur and are known risk factors of PONV.[9 20] Although risk factors are well defined for the population and are used to plan antiemetic therapy for a given individual, they unfortunately are not highly predictive.[30]

In children, there are fewer data than in adults regarding risk factors. However, Eberhart and colleagues[31] identified four risk factors: duration of surgery >30 min, age >3 yr, strabismus surgery, and history of postoperative vomiting in a parent, sibling, or the patient.

Pathophysiology of PONV

Emesis is believed to be governed by the emesis centre in the brain, which receives several afferent inputs (Fig. 1). Vagal input from the gut can activate the emetic centre, and also afferent action from the chemoreceptor trigger zone (CTZ). The CTZ sits outside the blood–brain barrier and contains several different receptors that modulate its activity. Most antiemetic medications act by either a direct or indirect antagonizing of emetogenic substances on receptors in the CTZ.

As there are several receptor systems involved in the development and treatment of PONV, it seems obvious that a combination of drugs acting at the different receptors would have greater efficacy than a single drug. Increasing the dose of a single class of drug does not necessarily decrease the incidence of PONV, especially in patients with risk factors.[32 33] Also, the incidence of side-effects increases as the dose increases in many drug classes (Table 1).[34] The multimodal technique therefore offers the benefits of enhanced PONV reduction with a lower incidence of side-effects.

Intuitively, the combined effects of drugs should be synergistic since each antiemetic intervention has a different mode of action. However, current data for the agents available indicate that the effects are simply additive.[9 35 36] This observation underscores the importance of risk-stratifying patients as noted above and a holistic approach emphasizing both pharmacological and non-pharmacological therapies.

Approach to multimodal therapy

Broadly, the multimodal approach constitutes both pharmacological and non-pharmacological therapies, which commences in the preoperative area and continues until discharge of the patient. In the preoperative area, minimizing anxiety is important. Anxiolysis with benzodiazepines has been shown to reduce PONV in several small studies.[37 38] Other interventions to minimize anxiety include optimizing information provided to the patient, a patient-friendly facility layout, and positive and compassionate interactions with staff. All of these interventions help minimize anxiety and likely reduce the incidence of PONV due to its impact on PONV.

Preoperative dexamethasone reduces the incidence of PONV.[39] Aprepitant (a neurokinin-1 antagonist) administered before anaesthesia is effective in reducing both vomiting and nausea for up to 48 h after surgery.[40 41] Pre-hydration with oral carbohydrate containing clear fluids up to 2 h before surgery also reduces PONV.[42] Similarly, adequate i.v. fluid resuscitation has become part of the multimodal regimen[43 44] with both crystalloids and colloids reducing PONV.[45] The choice of the type of fluid does not alter the incidence of PONV significantly.[46]

The intraoperative approach starts with minimizing factors that can increase PONV. Thus, the choice of anaesthetic is important. Inhalation anaesthetics, including nitrous oxide (dose-dependent), are associated with an increased risk of PONV. The use of regional anaesthesia decreases the incidence of PONV compared with general anaesthesia.[47] Although it would be ideal for patients at high risk for PONV/PDNV, regional anaesthesia is not always available as an option. Total i.v. anaesthesia (TIVA) decreases the incidence of PONV compared with inhalation anaesthetics and N_2O.[43] More specifically, the use of propofol as both an induction and maintenance agent (as TIVA) decreases the incidence of PONV,[6 48] but might be associated with higher cost.[6] Propofol has direct antiemetic effects and has been used after operation to treat PONV at doses of 10–20 mg. The minimum effective concentration of propofol for PONV is 300 ng ml^{-1}.[49] As patients usually wake up at propofol concentrations of 1000–2000 ng ml^{-1}, the antiemetic effect of propofol administered intraoperatively lasts for up to 30 min after operation.

Analgesia is a key component of intraoperative anaesthesia, with opioids as the mainstay of treatment. However, increasing intraoperative and postoperative opioid administration is associated with a much higher risk of PONV.[28] Short-acting opioids do not increase the incidence of PONV[50] when used as part of a TIVA regimen, but do not offer postoperative analgesia. Pain itself increases PONV, and thus the objective is to create the optimal balance between opioid administration and pain relief. There are several analgesic alternatives to opioids that have become available for i.v. administration in the last few years. Reducing the amount of opioids administered while obtaining good pain relief is the ultimate objective. Non-steroidal anti-inflammatory drugs (NSAIDs) decrease PONV compared

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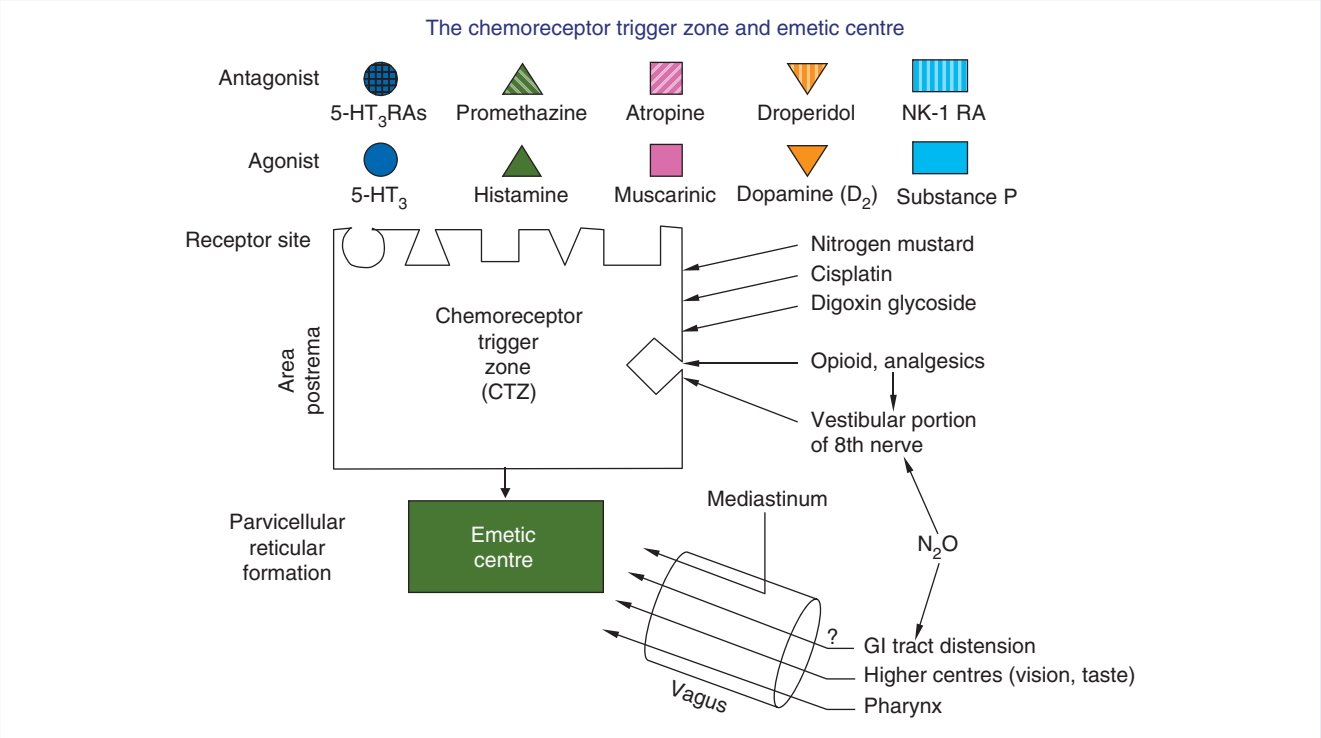

Fig 1 CTZ and emetic centre. With permission from Watcha and White.[73]

Table 1 Side-effects of commonly used antiemetics by drug class

Drug class	Side-effects
Serotonin antagonists	Headache, diarrhoea, constipation, arrhythmia
Neurokinin inhibitors	Dizziness, diarrhoea, headaches, weakness
Steroids	Dizziness, mood changes, nervousness
Antihistamines	Confusion, drying of mucosal membranes, sedation, urinary retention
Butyrophenones	Prolonged QT interval (at doses $\geq$0.1 mg kg^{-1}), hypotension, tachycardia, extra-pyramidal symptoms
Benzodiazepines	Sedation, disorientation

with opioids in numerous studies.[51–53] There are clear data for the opioid-sparing effects of NSAIDs and consequent reduction in PONV.[54] Small doses of i.v. ketamine also provide opioid-sparing[55] with a trend towards reducing PONV.[56] The opioid-sparing effects described above have a dual role of both reducing the incidence of PONV and enhancing overall pain management as described for multimodal analgesia below.

Reversal of neuromuscular block is required for many types of surgeries. Although multiple authors[23] have demonstrated that high-dose neostigmine increases the risk of PONV, a recent meta-analysis suggests no increased risk with neostigmine use.[57] This issue remains unclear, and more study is needed on this issue.

Intraoperative antiemetics form the cornerstone of antiemetic therapy[16] (Fig. 2). Apfel and colleagues[9] demonstrated that using one or more antiemetic therapies (up to 4) decrease the incidence of nausea and vomiting significantly (Fig. 3). This study showed that with each additionally administered antiemetic, the risk of PONV was further reduced by 30% (the so-called rule of 1/3). This extremely large study provides the foundation demonstrating the validity of the multimodal model.[58] Numerous studies have shown that two antiemetic therapies significantly decrease the incidence of PONV compared with single-drug prophylaxis in high-risk surgical populations.[59 60] Although there are data demonstrating the efficacy of different antiemetic therapies, too much of a good thing can be counterproductive. Recent data suggest that aprepitant, when added to three different antiemetics, might actually increase the incidence of PONV.[61] With a minimal cost and side-effects of the majority of antiemetics available, a more liberal approach than suggested by the Apfel criteria or the SAMBA (Society for Ambulatory Anesthesiology) guidelines has been proposed.[62]

Acustimulation at the P6 acupoint has been shown to be effective in preventing PONV.[63 64] A meta-analysis of acustimulation in pregnant patients has shown similar efficacy.[65] As part of a multimodal regime, acustimulation provides a further 30% reduction of PONV when combined with 4 mg ondansetron (i.e. similar efficacy as a second antiemetic).[66] There are smaller

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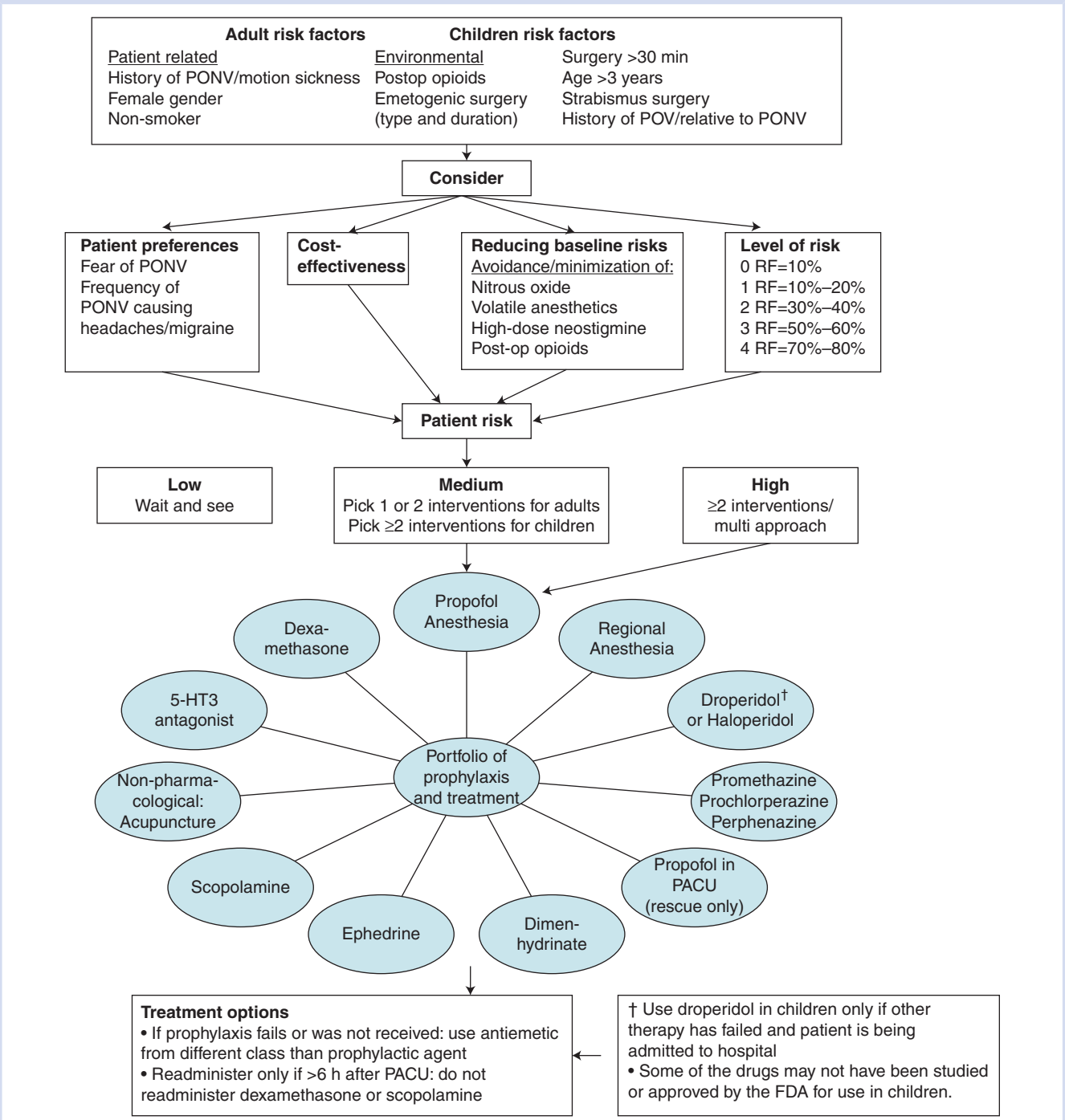

Fig 2 Algorithm for management of PONV. SAMBA guidelines for PONV from Gan and colleagues[16] with permission.

studies that demonstrate that acupuncture decreases PONV over 24 h;[67] however, data for PDNV are lacking.

PDNV is quite common after outpatient surgery.[5] However, risk factors for PDNV are likely to be quite different from those of PONV.[13] Thus, the antiemetics that are effective and the impact of multimodal therapy are also likely to be quite different. In a meta-analysis of PDNV, ondansetron and dexamethasone were more effective than placebo. However, droperidol did not seem effective for PDNV prophylaxis. In the few combination studies reviewed in this article, a combination of two drugs was more effective than a single drug. For example, the number needed to treat (NNT) with ondansetron 4 mg was 13, while for a combination of two antiemetics, the NNT was about 5. The authors concluded that the routine use of two or more antiemetics for PDNV in high-risk patients is justified.[11] The data on the efficacy of specific

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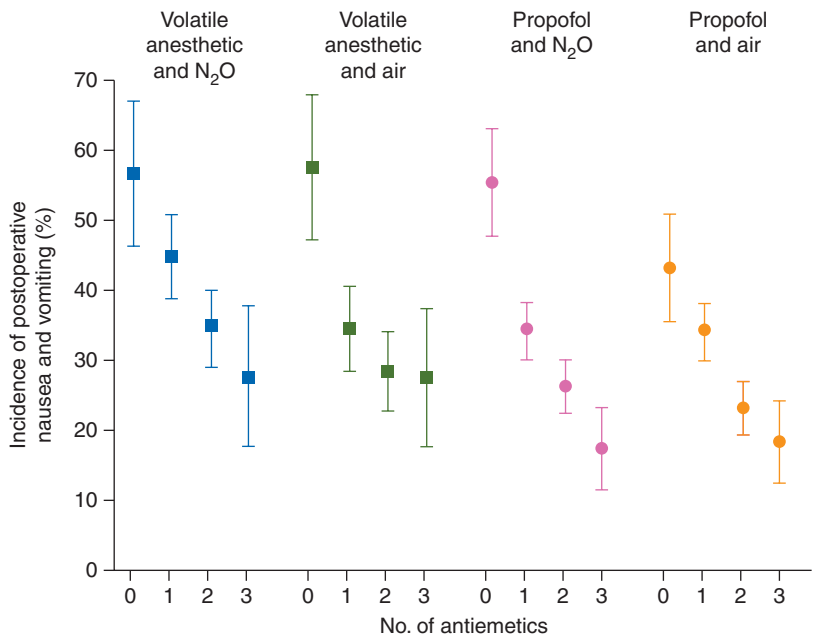

Fig 3 Effect of multiple antiemetic therapies. With permission from Apfel and colleagues. © Massachusetts Medical Society.[9]

antiemetics and their combination are still lacking, so definitive conclusions are difficult to make at present.

Conclusions

A planned multimodal algorithm starting in the preoperative area can significantly reduce the incidence of PONV. This includes both a strategy for risk assessment, risk reduction, and therapy targeted at matching the risk with the number of antiemetics administered. Most patients present with at least one Apfel criteria risk factor. As the cost both in money and side-effects is small with present antiemetics, the authors' preference is to start with a minimum of two antiemetics (generally dexamethasone 4 mg soon after induction and ondansetron 4 mg 20 min before the end of surgery). To this are added additional antiemetics depending on other risk factors. Unfortunately, the efficacy of the multimodal technique in preventing PDNV remains unclear. Although many of the same risk factors carry through to discharge, it is uncertain whether a similar multimodal approach to PDNV is similarly effective.

Multimodal approach to pain management

Despite advancements in the understanding of the pathophysiology of pain and pharmacotherapeutics, pain remains poorly treated in both the inpatient and ambulatory setting.[68] The importance of quantifying and treating acute postoperative pain is not only because of how unpleasant it is, but also because, if poorly treated, there is a risk for the development of chronic pain and its incumbent morbidity.[69]

Besides concerns of prolonged recovery and rehabilitation, pain still ranks among the highest patient and physician concerns for undesirable surgical outcomes.[1 2] The physiological consequences of pain can be quite deleterious to the patient. The incidence of mild-to-moderate pain after a variety of moderately invasive surgeries is about 62–65%[68] and the visual analogue scale remains >4 in about 10% of patients 7 days after discharge.[70] However, the incidence of the progression to chronic pain varies by surgery.[71] Today, acute postoperative pain is recognized to have two components, an earlier inflammatory component and a later neuropathic component. Just alleviating the inflammatory component in susceptible patients might not be sufficient; addressing the neuropathic pain component can be equally important in the prevention of chronic pain.[72]

Similar to the multimodal approach to PONV, the multimodal approach to pain management was conceived due to limitations in single-drug therapy, namely opioids and NSAIDs,[73 74] for which there is an increasing incidence of side-effects with increasing doses. Kehlet and Dahl[75] were the first to suggest that combining medications acting through different mechanisms lowers doses of analgesics, pain is better controlled, and there is a lower incidence of side-effects. This has since been demonstrated in multiple studies.[76–80] Again similar to PONV, the multimodal approach to pain management starts in the preoperative area.

Identification of risk factors for pain

Unlike PONV with the Apfel criteria, clearly quantifiable risk factors for postoperative pain have not been identified. While qualitative risk factors do exist, basing analgesic therapy on the number of risk factors is not feasible. However, identification of risk factors and assessment is

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still of paramount importance to minimize acute postoperative pain and progression to chronic pain.

Many patients who present for surgical procedures do so because of pain, and preoperative pain is a known risk factor for postoperative pain.[69] Therefore, a thorough preoperative assessment is essential. As alluded to previously, certain surgeries, namely Caesarean section, coronary artery bypass grafting, inguinal hernia repair, breast surgery, thoracotomy, and amputation, have a higher incidence of progression to chronic pain.[72 81]

Preoperative anxiety has been correlated with increased postoperative pain.[82 83] Despite this, the effect of preoperative benzodiazepine therapy on postoperative pain is unclear.[84 85] However, the incidence of side-effects from administration of benzodiazepines is low. Preoperative lorazepam results in reduced pain after abdominal hysterectomy,[86] and patients self-reported improvement in at least one other study with administration of preoperative midazolam.[87]

There have been several studies on genetic factors predisposing to both acute postoperative pain and its progression to chronic pain.[88] These are small studies without sufficient data to allow for individual patient stratification in the clinical setting.

Opioid tolerance stemming from long-term chronic opioid use is an important risk factor for increasing the complexity of treating postoperative acute pain. Thus, a quantification of opioid use in addition to bioavailability is important in the perioperative setting. Opioid management in these patients remains controversial; however, multimodal analgesia has been used successfully.[89]

Females require more analgesics[90] and are also more susceptible to developing chronic pain.[83] Several of the surgeries above are more common in women, and multimodal analgesia has been demonstrated to reduce the progression to chronic pain in these patients.[91 92]

Pathophysiology of pain

Although there are multiple definitions of pain, most experts agree that it is primarily a sensory experience.[72] There are two major components that contribute to perioperative pain, namely inflammatory and neuropathic pain. Both of these states share multiple common features and can be experienced either jointly or separately.[93]

A nociceptive stimulus from any source, whether thermal, mechanical, or otherwise, causes a release of multiple inflammatory substances in the affected tissue (Fig. 4). This leads to sensitization of nerves that supply the affected area, a phenomenon known as peripheral sensitization. Owing to afferent input to the central nervous system (CNS), the CNS also becomes sensitized, a phenomenon known as central sensitization. Both forms of sensitization are mediated through numerous neurotransmitters and feedback systems (Figs 4 and 5). These mechanisms are mainly protective in nature. The mechanisms involved in centrally mediated pain transmission are demonstrated in Figure 5. In general, as tissue heals the physiological changes ensuing from inflammatory pain resolve.

The progression from acute inflammatory pain to chronic neuropathic pain is poorly understood. There are three mechanisms that are central to the mediation of chronic neuropathic pain. First is the peripheral component with release of multiple inflammatory mediators responsible for the so-called 'positive symptoms', including hypersensitivity, allodynia, and erythema. Second is the central component, through the wind-up mechanism, that is mediated through the dorsal horn neurones and involves several areas of the CNS.[94] Third is the concept of central plasticity, in which both an excess of excitatory transmission and a loss of inhibitory transmission lead to an unfettered barrage of CNS input from the dorsal horn of the spinal cord.[95] Despite this highly simplified model, the pathophysiology of neuropathic pain remains poorly understood,[96] and multiple mechanisms remain to be elucidated.

The concept of pre-emptive analgesia focuses primarily on the early timing of analgesic therapy, whereas preventive analgesia focuses primarily on timing, duration, and efficacy of analgesic therapy.[97] A significant body of literature supporting pre-emptive analgesia has been withdrawn, thus creating ambiguity about the efficacy of this technique. The preventive model of analgesia has demonstrated clinical benefit,[98] and is the basis for the multimodal technique. The multimodal technique preserves total body nitrogen and enhances postoperative recovery and rehabilitation.[99 100]

Multimodal approach to pain management

Opioids still remain the mainstay of perioperative pain management (Fig. 6). While their judicious use offers analgesia through central and peripheral mechanisms, they are associated with many side-effects including an increased incidence of PONV, sedation, drowsiness, and pruritus, which delay discharge and add cost to postoperative care.[101 102] Additionally, there are animal data that demonstrate potentiation by opioids of tumour growth and tumour angiogenesis.[103] It is believed that this is regulated through the μ-opioid receptor.[104] A corollary for this concept has been drawn in breast and prostate cancer studies in two retrospective studies. When regional anaesthesia was used instead of postoperative opioid analgesia, the recurrence rate and metastases for breast cancer were lower, and the risk of prostate cancer recurrence was similarly decreased.[105 106]

NSAIDs, including COX-2 inhibitors, provide opioid-sparing (reduced opioid dosing requirements) and reduce some opioid-related side-effects.[52 107] Where bleeding is a concern for the surgical procedure (e.g. tonsillectomies), the use of non-selective NSAIDs should be avoided.[25 108] A meta-analysis suggested that the safety profile of selective COX-2 inhibitors in this setting can be useful.[109] After the withdrawal of several COX-2 products due to their long-term cardiovascular risks, their use in the acute postoperative setting was also called into question. An editorial suggests that there still clearly remains immediate and intermediate

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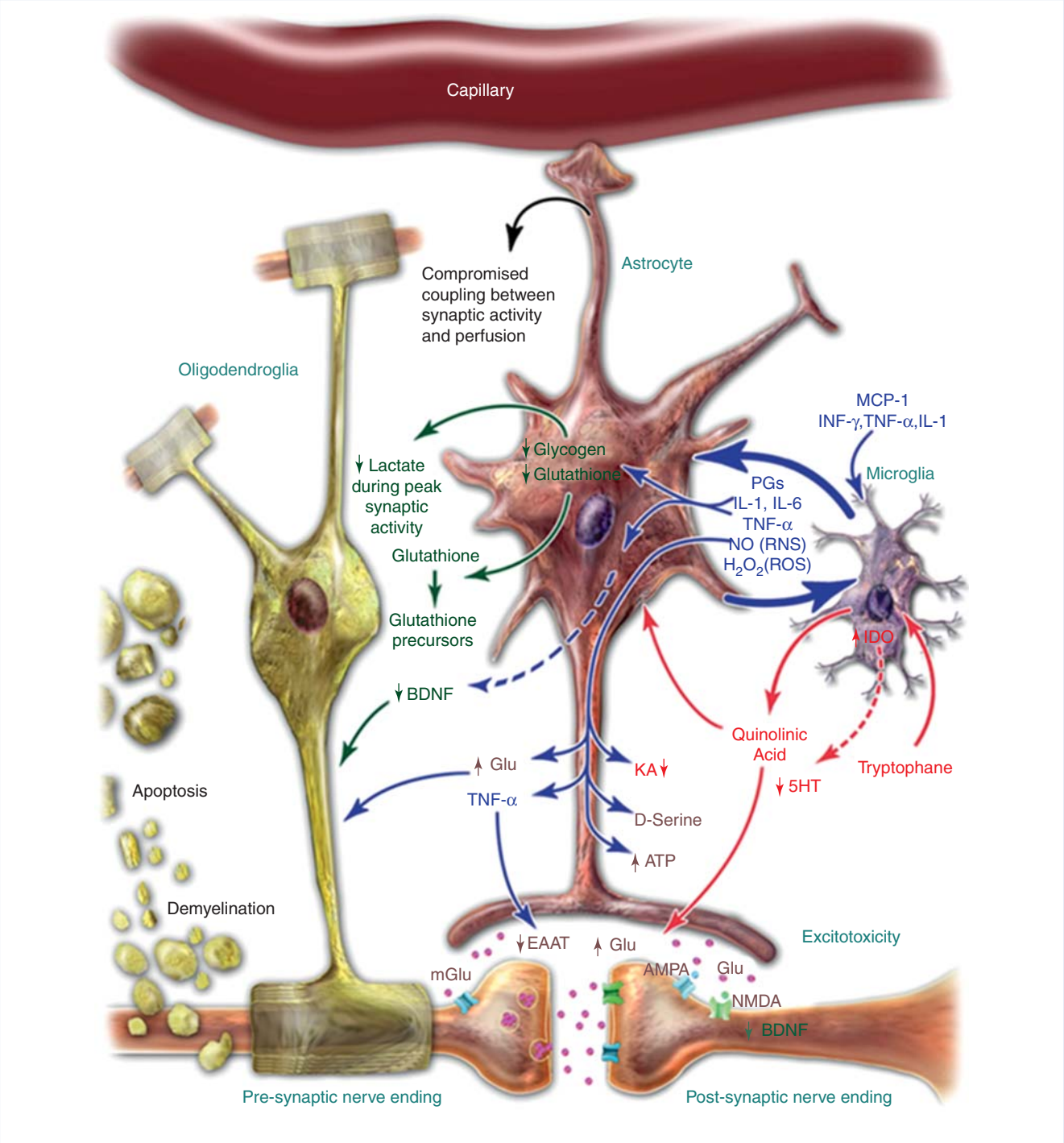

Fig 4 Microglia and inflammation. With permission from Maletic and colleagues (2009).[147]

benefit from COX-2 inhibition given for short durations such as postoperative pain, although long-term benefit remains unclear.[110] There is no increased cardiovascular risk in patients receiving short-term selective COX-2 inhibitors after non-cardiac surgery.[111] In one major study, when oral ibuprofen (non-selective NSAID) was compared with celecoxib (COX-2 inhibitor), they were both similarly efficacious in reduction of postoperative pain, constipation, and early need for rescue analgesia.[112] Thus, where bleeding is of minimal risk, non-selective NSAIDs are most appropriate, but where bleeding is a concern, a COX-2 inhibitor should be used.

Ketamine, because of its unique mode of action, has been studied extensively, especially in the orthopaedic literature. Small doses (0.15 mg kg^{-1} i.v.) improve recovery after outpatient arthroscopy.[113] In a large analysis, ketamine was

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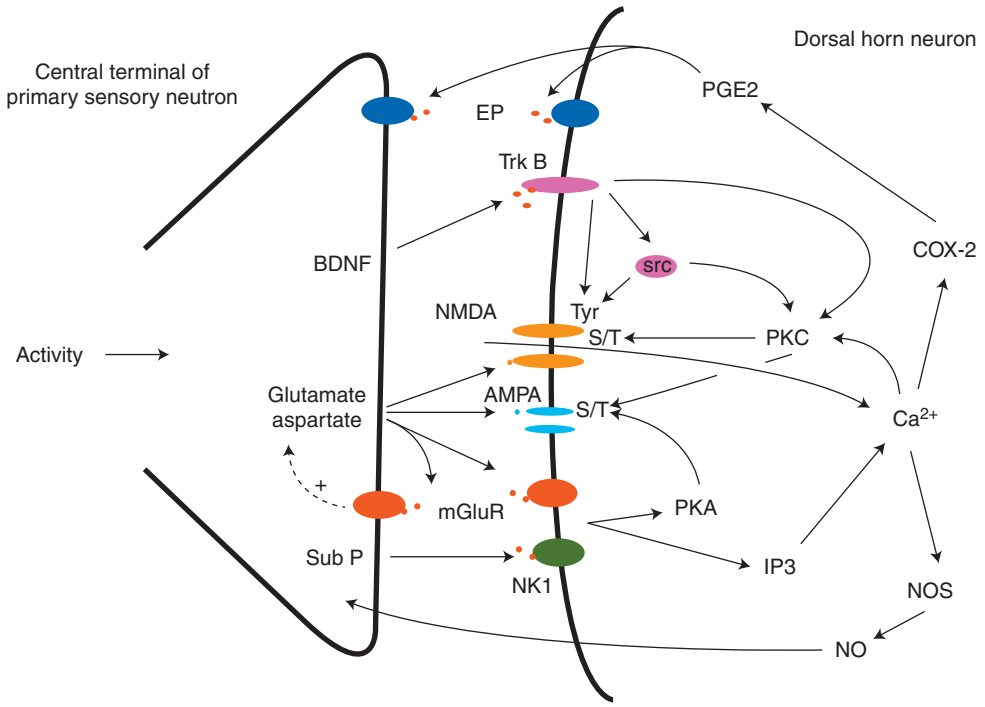

Fig 5 Mechanisms of central pain transmission. Reproduced from Costigan and Woolf (2000)[148] with permission from Elsevier.

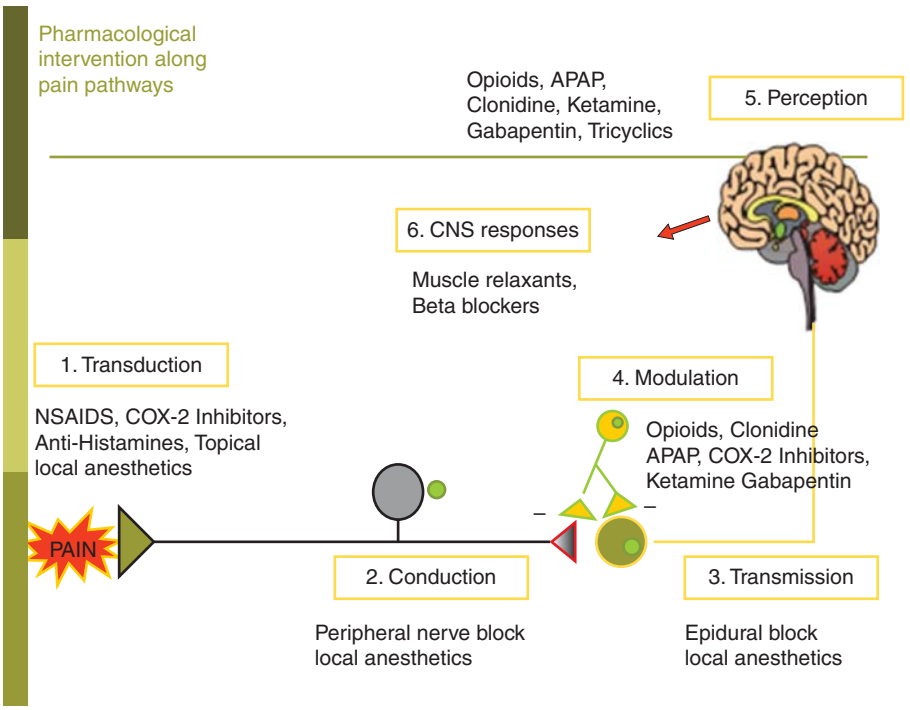

Fig 6 Multimodal approach to pain management. With permission from Raymond Sinatra, MD.

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opioid-sparing with a low incidence of side-effects.[55] When i.v. ketamine was added into a multimodal regimen that included postoperative epidural analgesia, the progression to chronic pain was reduced.[114] Also, ketamine added to an epidural multimodal regimen improved analgesia, demonstrating that its efficacy is not confined to the i.v. route alone.[115] The effects of oral ketamine on chronic pain are complex, and there are varying degrees of efficacy depending on the type of chronic pain.[116] Early administration of ketamine seems important in the prevention of chronic pain. Dextromethorphan is another *N*-methyl-D-aspartate-type glutamate receptor antagonist that prevents central wind up and has other antinociceptive mechanisms of action. Despite a fair number of studies on its use, the results remain conflicting.[101]

Gabapentin has been studied in multiple small trials that have been analysed in several large meta-analyses. Despite demonstrating opioid-sparing effects, superior acute postoperative analgesia, and a decrease in pain scores, a decrease in opioid-related side-effects was not noted.[117 118] The most favourable data with the fewest side-effects came from a single dose of 1200 mg of gabapentin given in the preoperative setting.[119] These effects have only been shown in the acute postoperative setting; gabapentin has not been shown to decrease the progression to chronic pain.[120 121] Pregabalin was evaluated as part of a multimodal regimen for total knee arthroplasty surgery, and was continued for 14 days into the postoperative period. There was a statistically significant reduction in chronic pain at 6 months; however, there was immediate peri- and postoperative confusion- and sedation-related issues that were attributed to dosing.[122] Similar to COX-2 inhibitors, several retracted articles on pregabalin bring its routine use into question as part of a multimodal regimen, and thus more studies are warranted. One might expect its actions to be similar to gabapentin. The antidepressant venlafaxine, when given before operation/perioperatively, reduced progression to post-mastectomy pain; however, the study did not use a multimodal analgesic regimen.[123] Therefore, more studies are needed with antidepressants before definitive conclusions can be made as to their role in preventive analgesia.

Two of the α-2 agonists have been studied as part of the multimodal regimen: dexmedetomidine and clonidine. Dexmedetomidine has shown to reduce opioid-related side-effects, enhance analgesia, and was devoid of side-effects when used for acute postoperative pain control as part of an i.v. patient-controlled analgesia regime.[124] When used for postoperative analgesia and recovery, dexmedetomidine plus morphine compared with morphine alone demonstrated an additive effect.[125] Dexmedetomidine as part of a perioperative analgesic regimen decreases opioid requirements, PONV, and postoperative stay.[126] I.V. clonidine, on the other hand, has not demonstrated any efficacy in the treatment of postoperative pain.[127 128] However, when used via the neuraxial route, clonidine as part of a multimodal regime is effective in reducing both acute postoperative pain and progression to chronic pain.[129]

Regional anaesthesia, whether neuraxial, via a peripheral nerve block, or both, is an important component of a multimodal regimen. When using regional anaesthesia, it is not only the modality, but also the duration of therapy that is important. Local anaesthetic administration into the wound has been studied as part of multimodal regimens in laparoscopic surgeries. Although there are benefits in the immediate postoperative period (up to 4 h), these differences are less pronounced over time.[130 131] The results from single-shot peripheral nerve block studies also substantiate this effect, with early postoperative pain relief, but a high percentage of patients require adjuvant pain therapy at 24 h and up to 7 days.[132] When continuous perineural catheters (from 2 to 7 days) were used in combination with NSAIDs, postoperative analgesia beyond 24 h was very good.[133] Clonidine, when added as part of a single-shot upper extremity nerve block, enhances the duration of action of the block.[134]

In a meta-analysis, the use of regional anaesthesia decreased all-cause mortality and multiple morbidity indices.[135] Therefore, the use of neuraxial anaesthesia when appropriate might have several effects independent of pain control. Epidural anaesthesia (continued after operation) combined with general anaesthesia was superior to general anaesthesia alone in multiple outcomes.[136] There are also data to indicate that in thoracotomy surgeries, which are at high risk for chronic pain, the use of perioperative epidural analgesia decreases the incidence of chronic pain.[137] Neuraxial analgesia is not beneficial in reducing the progression to chronic pain for all high-risk surgeries; however, the studies are small and further data are needed.[138] Spinal anaesthesia compared with general anaesthesia for hysterectomy decreased the incidence of chronic pain in one retrospective analysis.[139] Nitrous oxide has also been suggested to reduce the incidence of progression to chronic pain; however, further study is needed.[140]

There is value to using several pharmacological agents as part of a neuraxial block. The addition of clonidine to a bupivacaine/fentanyl solution significantly reduced pain, but side-effects were noted to be dose-dependent for increasing clonidine.[141] Concerns over hypotension have limited use of clonidine in the obstetric population. However, at least one study did not demonstrate adverse sequelae due to this.[142] The optimal combination of bupivacaine, fentanyl, clonidine, and infusion rate has been determined. The combination that provided the greatest pain relief at the lowest infusion rate was 9 mg h^{-1} bupivacaine, 21 μg h^{-1} fentanyl, and 5 μg h^{-1} clonidine infused at 7 ml h^{-1}.[143]

Postoperative pain can also be reduced by non-pharmacological adjuvants. Transcutaneous electrical nerve stimulation (TENS), when used at sub-noxious frequency over the wound area, reduces postoperative analgesic consumption.[144] Peri- and postoperative wound cooling significantly reduces postoperative analgesic consumption without an increase in wound infections.[145] Studies have suggested a role of heat in peripheral sensitization.[146] However, further studies are needed for all of the above modalities before definitive conclusions can be drawn.

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In summary, the anaesthetic pain regime should start in the preoperative area with patient assessment and detailed communication with the surgeon about the type of surgery and the proposed approach. The more qualitative risk factors a patient possesses, the more aggressive the anaesthesiologist should be in their preventative pain management. Regional anaesthesia, either neuraxial or peripheral nerve block, should always be considered where feasible. Breakthrough pain is well described in the chronic pain and cancer literature, and it similarly occurs in the acute postoperative situation. It is best managed with a rapid onset, short-lasting agent (e.g. fentanyl in the recovery room) or an agent of a different class than those previously administered.

For expectant mild pain from minor surgery, the authors recommend acetaminophen, NSAIDs, or both, local anaesthetic wound infiltration, and intraoperative opioid therapy. Non-pharmacological therapy (e.g. TENS, cooling packs) should also be used when appropriate after operation.

For expected moderate pain, the authors suggest two to three agents to be used intraoperatively, including regional anaesthesia. A combination of opioids and NSAIDs should also be considered for postoperative pain management.

For expected severe pain, the authors suggest that regional anaesthesia be strongly considered unless contraindicated, with a multiagent infusion and leaving the regional catheter in place. Intraoperative management should also consist of aggressive multimodal agent regimen, with prompt attention and treatment of postoperative pain.

In patients with a history of chronic opioid use or where the risk of chronic pain is high, both ketamine and regional anaesthesia should be considered both intraoperatively and after operation.

Conclusions

A planned multimodal approach to pain management can significantly reduce acute postoperative pain and its progression to chronic pain. Blockade of both peripheral and central sensitization through the use of multiple agents and approaches is critical. The number of agents is important; however, the duration of therapy is also critical to ensure that analgesia is continued into the postoperative period to ensure mobilization and recovery. While there are data to support several individual agents and modalities in reducing progression to chronic pain, further study is needed to delineate the exact risk factors and optimal drug combinations in preventing chronic pain.

Conflict of interest

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