



REVIEW

The Routes of Administration for Acute Postoperative Pain Medication

Filomena Puntillo · Mariateresa Giglio · Giustino Varrassi

Received: February 3, 2021 / Accepted: June 24, 2021 / Published online: July 17, 2021
© The Author(s) 2021

ABSTRACT

Effective treatment of postoperative acute pain, together with early mobilization and nutrition, is one of the perioperative strategies advocated to improve surgical outcome and reduce the costs of hospitalization. Moreover, adequate pain control reduces perioperative morbidity related to surgical stress and can also prevent the incidence of chronic postoperative pain syndromes, whose treatment is still a challenge. The choice of the most appropriate analgesics depends not only on the drug class, but also on the most suitable route of administration, the best dosage for that route, and unique limitations and contraindications for every patient. In the present review, a comprehensive analysis was performed on the different routes of administration of acute postoperative pain medications and their indications and limitations, focusing on recent evidence and international recommendations.

F. Puntillo (✉)
Department of Interdisciplinary Medicine, “Aldo Moro” University of Bari, Bari, Italy
e-mail: filomena.puntillo@uniba.it

F. Puntillo · M. Giglio
Intensive Care and Pain Unit, Policlinico Hospital,
Bari, Italy

G. Varrassi
Paolo Procacci Fdn, Via Tacito 7, 00193 Roma, Italy

Keywords: Postoperative pain; Route; Drugs; Opioids; NSAIDs; Paracetamol; Anesthetics

Key Summary Points

A multimodal analgesic approach that encompasses a variety of analgesic and non-pharmacological interventional techniques ensures better pain control than a single intervention

The knowledge of indications and limitations of the different routes of administration of acute pain drugs could help to achieve better pain relief

The oral route is the way of choice, unless contraindicated, while the intramuscular route is strongly discouraged

Epidural analgesia is strongly recommended for patients who undergo major thoracic and abdominal procedures, hip surgery, and lower extremity surgery, particularly in patients at risk for cardiac or pulmonary complications, or prolonged ileus

Peripheral blocks are recommended for surgery at the extremities and in abdominal, breast, or thoracic surgery

Accurate monitoring is needed in all cases in order to prevent complications

INTRODUCTION

Acute pain has been recently defined as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” [1], and often requires a multimodal approach.

Multimodal analgesia comprises a variety of analgesic medications and techniques targeting different mechanisms of action at peripheral or central sites of the nervous system. Thanks to an additive or synergistic effect, pain relief obtained through a multimodal approach is more effective than that with a single-modality intervention. Systemic opioids might not be necessary in all cases [2–4], and limited evidence suggests that perioperative opioid therapy is associated with an increased likelihood of long-term opioid use [5]. Randomized trials have shown that multimodal analgesia is associated with superior pain relief and decreased opioid consumption compared with the use of a single medication administered through one technique [6–8].

In the setting of multimodal analgesia, the choice of route may be determined by various factors, including the pain type, its severity and location, patient preference, or conditions. Other important factors to consider are the speed of analgesic effect, the duration of action, the ease of use, patient compliance, and costs.

The aim of this review is to summarize the available evidence on acute postoperative pain treatment outlining the advantages and limitations of each route.

METHODS

Starting from existing international guidelines on postoperative pain management in surgical adult patients, we checked Pubmed, Embase, and the Cochrane Library databases for additional recent studies (range 2015–2020), including meta-analyses, reviews, and clinical studies, and excluding case series and case reports. The search strategy included the following Medical Subject Heading (MeSH) terms: postoperative pain, oral medication,

intravenous medications, epidural route, intrathecal route, opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, local anesthetics, peripheral blocks, adjuvants. A total of 1835 study titles and abstracts were screened, with 80 selected for further review. Additional articles identified by review of original article reference lists were included. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

A summary of strength and quality of main recommendations from recent guidelines is provided in Tables 1 and 2.

ROUTES OF ADMINISTRATION

Oral Route

Oral administration of analgesic agents is simple and noninvasive and has shown good efficacy in most settings, with high patient acceptability and similar efficacy as the IV route. Vomiting or delayed gastric emptying are a contraindication to oral administration. Indeed, if the oral route is used postoperatively before the return of normal gastric motility, the “dumping effect” can occur, i.e., accumulated doses may enter the intestine at the same time once emptying resumes, resulting in a sudden large systemic uptake of analgesics with an increased risk of adverse events (AEs). The type of analgesic formulation (suspension or tablet) and the type of preparation (immediate or slow release) can affect intestinal absorption and bioavailability, which in turn depends on the effects of first-pass hepatic metabolism of the different drugs [9]. As a consequence, for postoperative pain control, immediate-release formulations of every drug class are preferred.

A “league table” of analgesic efficacy has been proposed [9] based on randomized, double-blind studies or meta-analysis in patients with moderate to severe pain. It estimates the number of patients that need to be treated (NNT) in order to obtain a visual analog scale (VAS) reduction of at least 50% in one patient compared with placebo.

Table 1 Recommendations for postoperative analgesia

Recommendation	Strength of evidence	Quality of evidence
Perioperative multimodal analgesia, i.e., the use of a variety of analgesics and techniques combined with non-pharmacological interventions, is recommended in children and adults	Strong	High
Oral versus IV opioids in patients who can use the oral route	Strong	Moderate
Against IM route	Strong	Moderate
IV opioids PCA when parenteral route is needed	Strong	Moderate
Against routine basal infusion of opioids with IV PCA in opioid-naïve adults	Strong	Moderate
Need for appropriate monitoring of sedation, respiratory status, and other AEs in patients who receive systemic opioids	Strong	Low
The use of paracetamol and/or NSAIDs (as part of multimodal analgesia) in patients without contraindications	Strong	High
Against prescribing a NSAIDs or COXIBs in patients at risk of renal hypoperfusion	Strong	High
An estimated clearance of plasma creatinine below 50 mL/min is a contraindication to NSAIDs/COXIBs	Strong	High

Table 1 continued

Recommendation	Strength of evidence	Quality of evidence
Against using COXIBs in patients with a history of atherothrombosis (peripheral artery disease [PAD], stroke, or myocardial infarction)	Strong	High
Against administering NSAIDs for more than 7 days in patients with peripheral artery disease, stroke, and myocardial infarction	Weak	High
Against associating NSAIDs with therapeutic doses of anticoagulant	Weak	Low
Neuraxial analgesia for major thoracic and abdominal procedures, particularly in patients at risk for cardiac complications, pulmonary complications, or prolonged ileus	Strong	High
Provide appropriate monitoring of patients who have received neuraxial analgesia	Strong	Low

IV intravenous administration, *IM* intramuscular, *PCA* patient-controlled analgesia, *AEs* adverse events, *NSAIDs* nonsteroidal anti-inflammatory drugs, *COXIBs* selective COX2 inhibitors

Opioids

Opioids act on three types of opioid receptors, namely MOR (μ), DOR (δ), and KOR (κ), with variable affinity to individual types of opioid receptors and interactions with these receptors (agonists, partial agonists, antagonists). They exert analgesic effects, influence mood and behavior, and affect respiratory, cardiovascular, gastrointestinal,

Table 2 Summary of recommended drugs and routes of administration for postoperative pain

Drugs/routes	Postoperative pain intensity		Comments
	Mild acute pain (NRS < 4)	Moderate to severe acute pain (NRS > 4)	
Oral paracetamol	Recommended	Recommended*	Consider the high variability in plasma concentration *In combination with opioids
IV paracetamol			Consider IV when an oral route is not possible, but higher risk of arterial hypotension
Oral NSAIDs/COXIBs	Recommended	Recommended*	Check for contraindications, higher risk of AEs in coronary bypass and in elderly with hip fracture *In combination with opioids
IR oral opioids		Recommended	Consider dose adjustments to promote functional recovery and monitor AEs
CR oral opioids		Not recommended	
IV opioids PCA		Recommended	Consider adequate cognitive function and increased risk of AEs
Continuous IV opioids ± PCA		Not recommended	
Continuous epidural opioids and local anesthetics infusion		Suggested	Consider in case of thoracic, upper abdominal and lower limb surgery, complex spine surgery, high risk patients or cognitive impairment
IT bolus of opioids and local anesthetics		Suggested	AEs are more frequent with IT than with IV opioids
Oral gabapentinoids		Suggested	Consider if severe pain is expected and to reduce opioid consumption
IV small doses ketamine		Suggested	In combination with opioid or in case of opioid hypersensitivity
Paravertebral block or pectoral nerves block		Recommended in major breast surgery and liver resection	For minor breast surgery, local anesthetic wound infiltration is indicated

Table 2 continued

Drugs/routes	Postoperative pain intensity		Comments
	Mild acute pain (NRS < 4)	Moderate to severe acute pain (NRS > 4)	
Continuous wound local anesthetic infusion and/or fascial plane blocks such as transversus abdominis plane or quadratus lumborum blocks		Recommended in cesarean section and in major abdominal surgery, except for laparoscopic cholecystectomy	For abdominal surgery, fascial plane blocks are superior to wound infiltration
Thoracic paravertebral block		Suggested for thoracotomy	Similar effect in comparison to TEA

NRS numeric rating scale, *NSAIDs* nonsteroidal anti-inflammatory drugs, *COXIBs* selective COX2 inhibitors, *IR* immediate-release formulation, *CR* controlled-release formulation, *AEs* adverse events, *IV* intravenous, *PCA* patient-controlled analgesia, *IT* intrathecal, *TEA* thoracic epidural analgesia

neuroendocrine, and immune systems [10]. It should be borne in mind that the majority of opioids cause immunosuppression, which can result in an increased risk of postoperative infections [11] and possible opioid-induced hyperalgesia (opioid paradox), manifesting as increasingly severe pain despite opioid dose escalation [8].

Oral opioids have been used to manage moderate to severe postoperative pain, both as immediate-release (IR) and controlled-release (CR) formulations. They are effective in the treatment of acute pain, like opioids given by other routes, if equianalgesic doses are administered. Agents differ by breakdown products, time of onset, time of peak effect, and duration of effect. Routes alter the time of onset, the time of peak effect, the duration of action, and the dose required relative to the parenteral form.

In most cases only short-term opioid therapy is indicated. All patients who receive opioids for postoperative analgesia should be monitored closely in the initial hours after surgery or after subsequent dose changes. Clinicians must assess alertness and signs or symptoms of hypoventilation or hypoxia, but also nausea, vomiting, and opioid-induced constipation, pruritus, and urinary retention. Risk factors for respiratory depression include obstructive or central sleep

apnea and use of other central nervous system depressant medications. In the case of sedation or respiratory depression, a reduction or cessation of the opioid, respiratory support, and opioid antagonist administration may be necessary. The incidence of AEs is usually dose-related and is associated with an increased in hospital stay and costs [12], so both pharmacological (i.e., HT3 antagonist, dexamethasone or droperidol for nausea and vomiting, or opioid antagonists for constipation) and non-pharmacological strategies (i.e., reduced doses, multimodal analgesia, and acupuncture for nausea) should be adopted to prevent them [9]. At discharge, the duration of therapy and a strategy for the weaning of opioids must be planned, and the potential for their abuse or misuse should be considered.

Immediate-Release Formulations Oral IR formulations of opioids have an onset time of about 30 min and reach the maximum effect at 1–2 h [13]. Usually, they are combined with paracetamol and NSAIDs in order to increase their effectiveness. A single dose of 60 mg of codeine, with a NNT of 12, does not adequately control postoperative pain [14] since it has no effect in 40% of patients, while when combined with 1000 mg of paracetamol, its NNT decreases

to 2.2 and the duration of analgesia is extended by approximately 1 h [15].

Oral tramadol provides good postoperative pain control: NNTs are 7.1, 4.8, and 2.4 at doses of 50, 100, and 150 mg, respectively [16], even if a large difference in bioavailability of a single dose of tramadol has been described (up to 30%). The combination of tramadol and paracetamol allowed for better pain control than single medications [17].

Oral 5 mg oxycodone has no advantage in comparison to placebo in moderate and severe acute pain [18], while oxycodone 15 mg or combinations of oxycodone [5–10 mg] plus paracetamol (325–1000 mg) have a significant analgesic effect. The lowest NNT of 1.8 is obtained with the combination of 10 mg oxycodone and 1.000 mg of paracetamol. The combination of oral oxycodone 5 mg plus 400 mg ibuprofen showed comparable effects [19].

Twenty milligrams of oral IR morphine (with subsequent 10 mg doses as needed) is more efficacious in postoperative pain control for hip surgery than 5–10 mg of IM morphine, as needed, after starting an IV bolus of morphine [20].

IR oral opioids such as oxycodone, morphine, and tramadol have also been used as “step-down” analgesics; doses were calculated based on prior patient-controlled analgesia (PCA) or epidural analgesia requirements.

Tapentadol IR has strong analgesic efficacy in moderate to severe pain after multiple post-surgical settings, with few side effects [21].

Methadone is a synthetic opioid that has specific indications for patients addicted to opioids, while great caution should be exercised in acute pain treatment. A recent meta-analysis [22] showed that intraoperative methadone led to lower opioid consumption and pain scores compared to other opioids by other routes. However, its unpredictable and long half-life and the increased risk of AEs such as respiratory depression and arrhythmia still represent important caveats to its use [22].

Controlled-release formulations CR formulations (both slow-release and prolonged-release) may take 3–4 h or more to reach peak effect, so a rapid titration is easier and safer to reach with

IR formulations. Therefore, CR opioid preparations should only be used at predefined time intervals, usually for chronic pain, and IR opioids should be used for acute pain and for titration of CR opioids.

After total knee replacement, oral prolonged-release oxycodone/naloxone shows similar efficacy in pain control as IV morphine PCA, with a similar incidence of postoperative nausea and vomiting [23]. Moreover, the incidence of constipation is increased with CR oxycodone [24].

As a result of the above evidence, CR opioids are not indicated for the early management of acute pain due to their potential for AEs including lethal respiratory depression, as well as the risk of misuse after the patient has been discharged [25].

Paracetamol

The mechanism of analgesic action of paracetamol is complex, including the inhibition of COX activity and the modulation of descending serotonergic inhibitory pathways and of the cannabinoid system [26].

Single doses of paracetamol alone successfully control mild postoperative pain even if there is no good evidence for a dose-dependent analgesic effect of oral paracetamol. In fact, the NNT is 3.5 for 500 mg, while for a dosage of 1.000 mg the NNT is 3.6 [9]. The oral bioavailability of paracetamol is good, with oral absorption of effervescent tablets faster than the standard tablet. However, its plasma concentrations can vary significantly and remain sub-therapeutic in some patients.

Oral paracetamol is less effective, with a slower onset, than IV paracetamol, but it is more effective with a faster onset than paracetamol administered by the rectal route, when the same doses are considered.

Nonselective NSAIDs and COXIBs

NSAIDs belong to the group of non-opioid analgesics with anti-inflammatory, analgesic, and antipyretic action. They achieve these effects via inhibition of inducible nitric oxide synthase expression and NF-kappa B activation, activation of the system of lipoxins, and inhibition of substance P activity [27].

A number of NSAIDs and selective COX2 inhibitors (COXIBs) have been used to manage postoperative pain either alone or in combination with opioids. Their NNTs are dose-dependent and range from 2.7 for ibuprofen 600 mg to 2.4 for diclofenac 100 mg fast-acting, 2.7 for naproxen 500 mg and piroxicam 20 mg, 2.9 for ibuprofen 200 mg, and 2.5 for celecoxib 400 mg. NNTs of oral ketorolac, the most commonly used NSAID for postoperative pain, range between 1.8 for 20 mg and 2.6 for 10 mg [9]. In general, there is no difference in the analgesic effects or AEs between oral and IV or rectal NSAIDs in postoperative settings [28]. Recent National Institute for Health and Care Excellence (NICE) guidelines [29] further support the benefit of both NSAIDs and COXIBs in pain relief and rescue medication, with no clinically relevant difference in AEs but with similar opioid sparing effects.

Moreover, the comparison of different NSAIDs revealed a nonsignificant difference in pain control, rescue medication, and AEs between ketorolac versus diclofenac, diclofenac versus celecoxib, and ibuprofen versus celecoxib, while a clinical benefit is retrieved in pain control up to 24 h with naproxen compared to ibuprofen (moderate quality of evidence). The use of opioids was also reduced with ibuprofen compared to ketorolac (high quality of evidence). Ibuprofen was found to be less costly, and traditional NSAIDs were less costly in comparison to COXIBs. Given their well-known potential of increasing renal injury, the use of NSAID or COXIBs is discouraged in those patients with other risk factors, such as a pre-existing renal failure (i.e., clearance of plasma creatinine below 50 mL/min) or in the presence of renal hypoperfusion [30, 31]. Moreover, NSAIDs are not recommended for pain management in hip fracture in the elderly, because of the increased risk of upper gastrointestinal bleeding, nephrotoxicity, and fluid retention in this specific population [32].

The atherothrombotic risk associated with COXIBs is well documented [33, 34], and NSAIDs are contraindicated for management of perioperative pain in patients who undergo coronary artery bypass graft surgery, because of an increased risk of cardiovascular events [35].

According to a recent meta-analysis [36], NSAIDs with dexamethasone are not associated with an increased risk of hemorrhage. However, the combination of NSAIDs and a therapeutic dose of anticoagulants (enoxaparin, rivaroxaban, or vitamin K antagonist) was shown to lead to a 2.5-fold increased risk of severe hemorrhage [37].

Recently, conflicting evidence is emerging on the use of nonselective NSAIDs and the risk of anastomotic leakage after colorectal surgery [38, 39], due to the high heterogeneity of the population enrolled, the outcome definition, and the type of surgery. A large prospective multicentric study found that NSAIDs are not associated with increased anastomotic leak rate or acute kidney injury and confirmed a significant reduction of strong opioid needs [40].

Gabapentinoids

Gabapentinoids are widely used in managing neuropathic pain. Several mechanisms are now known about their action, such as depressed neuronal excitability due to the interaction with the 2D1 calcium channel subunit, increased descending inhibition, inhibited descending serotonergic facilitation, and modulation of the affective component of pain [41]. An increased interest has emerged in the last decade about their use in the perioperative phase. Early evidence suggested that oral gabapentin and pregabalin reduced opioid consumption in the early postoperative period [42], and the American Pain Society recommended their use in the context of multimodal perioperative analgesia [2]. However, a recent meta-analysis finds no clinically meaningful difference in pain at 6–24 or 48 h, with lower risk of postoperative nausea and vomiting and greater risk of dizziness and visual disturbance, with a very large range of the doses reported ranging from 300 to 1200 mg for gabapentin and from 75 to 300 mg for pregabalin, given either preoperatively or postoperatively [43]. Recent NICE guidelines [29] noted that opioid consumption was significantly reduced with oral gabapentin and pregabalin, with similar AEs, but again, the large variability in the doses adopted limited the evidence.

Intravenous (IV) Route

The IV route is the fastest route of administration of analgesics; however, the costs of intravenous opioids, paracetamol, or NSAIDs are higher, with no benefit in terms of pain control. Therefore, the IV route of administration should be used only if the oral route is not possible.

Opioids

Intermittent IV bolus doses are suggested for titration of opioids for severe acute pain, because this approach ensures rapid onset without the uncertainty of medicine absorption by other routes. There is no clear consensus on the optimal doses and dose intervals [44]. The titration of IV bolus doses of an opioid is frequently done with an “age-based” strategy at intervals of 3–5 min. Age, rather than patient weight, appears to be a better determinant of the amount of opioid an adult is likely to require for effective management of acute pain [9].

No difference in pain control or the need for rescue medications between oral (IR formulations) and IV opioids has emerged in literature, while one study suggested increased harm with IV opioids, with a higher incidence of pruritus [29].

For morphine, boluses of 2–3 mg given at 5-min intervals as needed were more effective than the same doses given at 10-min intervals, with no difference in AEs.

With an approximate “1+1” titration protocol of hydromorphone (1 mg bolus followed by another 1 mg at 15 min if needed), a reduction in oxygen saturation (< 95%) was reported in 30% of patients [45]. Compared with a single dose of 2 mg IV, the “1+1” protocol had an opioid-sparing effect, because 42.3% of patients required only the first bolus, with the same efficacy.

Sufentanil (IV bolus of 0.15 mcg/kg followed by 0.075 mcg/kg every 3 min) was as effective as the equianalgesic bolus doses of IV morphine in acute pain in emergency department and less effective at 6 h [46]. IV sufentanil was as potent

as oxycodone in postoperative pain but leads to more episodes of nausea and vomiting [47].

In dental surgery, better pain control was achieved with IV tramadol than the same oral dose, but IV tramadol can result in a high incidence of nausea and vomiting [48]. This effect can be controlled by slowing delivery of the medicine or by administering it before the patient wakes up from anesthesia.

Oxycodone IV exhibited better analgesic efficacy when compared to fentanyl and sufentanil, while its efficacy was comparable to morphine. However, more side effects were evidenced with oxycodone than with fentanyl [49].

Continuous IV Opioid Infusion The aim of a continuous IV infusion of opioids is to avoid the oscillations in plasma concentration linked to intermittent administration, ensuring constant blood levels. Even if a continuous infusion can be regarded as an appealing strategy to control acute pain, especially in those patients who cannot take medications orally, many factors could affect its real efficacy, such as variation in patient response and variable intensity of acute pain. Lastly, the effects and the AEs of any modification of the infusion rate are not immediate. Therefore, continuous IV opioid use is rarely necessary and only in patients who demonstrate a need for round-the-clock dosing of IV opioids, while PCA is a good option for patients who will require analgesia for more than a few hours and have adequate cognitive function to understand how to use the device [29]. PCA with a continuous background infusion increases the risk of nausea, vomiting, and respiratory events in comparison to PCA alone in adults [9].

Paracetamol

Paracetamol IV has a good analgesic profile after surgery with an NNT of 4.0 over 4 h and an NNT of 5.3 over 6 h [50]. When a single IV dose has been combined with opioids, it reduced opioid requirements by 30% over 4 h [51]. The use of the oral form is suggested, due to the good bioavailability and tolerability, limiting the use of the IV form. Recent guidelines [29] confirm the nonsignificant difference between IV and

oral formulations in terms of pain scores, rescue medication, and AEs, with reduced costs of oral paracetamol. The risk of hepatotoxicity from therapeutic doses of paracetamol is extremely low, while the risk of hypotension is reported, particularly with IV formulations in critically ill patients [52].

NSAIDs and COXIBs

IV formulations of NSAIDs or COX-2 selective inhibitors are more expensive than oral or rectal ones while efficacy and incidence of AEs are similar [29].

IV or intramuscular (IM) ketorolac is an effective drug of multimodal analgesia: 60 mg is more effective than 30 mg (NNT for IM ketorolac is 1.8 for 60 mg and 3.4 for 30 mg). IM formulations seem to have a greater opioid-sparing effect than IV [53]. When added to PCA morphine, ibuprofen IV improved postoperative analgesia, with an opioid-sparing effect only when 800 mg was used [54]. Parecoxib, both IV and IM, has been shown to be effective [55]. The route of administration does not seem to alter the efficacy.

Co-administration of IV ibuprofen and paracetamol provided a superior analgesic effect over comparable doses of both monotherapies without an increase in AEs [56].

Ketamine

Ketamine is a phencyclidine derivative that is a competitive antagonist of glutamatergic NMDA receptors and inhibits HCN1 ion channels. Its analgesic action is mediated via inhibition of NMDA receptors in nociceptive neurons and activation of descending inhibitory monoaminergic pain pathways. Low doses of ketamine can reduce NMDA receptor-mediated secondary hyperalgesia and the wind-up phenomenon, thus reducing the risk of increased pain sensitivity and opioid tolerance [57]. Its metabolism is predominantly hepatic via the cytochrome P450 enzymes. Both its analgesic effects and AEs are dose-related. Its AEs are dose-dependent and include hypersalivation, nausea and vomiting, hallucinations, nightmares, and delirium. For analgesic purposes, sub-anesthetic doses of ketamine have been used (a bolus dose

of 0.25 to 1 mg/kg IV during or immediately after surgery), and a recent Cochrane review [58] noted that perioperative intravenous ketamine administration resulted in 19% reduction in postoperative opioid consumption and 19% reduction of pain 24 h after surgery, with no effects on nausea and vomiting. Recent guidelines re-assessing the evidence suggest its use in moderate to severe pain in combination with opioid or in the case of opioid hypersensitivity [29], since there was a significant reduction in opioid consumption when the combination was used.

Intramuscular and Subcutaneous Route

The IM and SC routes are commonly employed for the treatment acute pain.

However, after surgery, other routes are to be preferred because conditions of poor perfusion such as hypovolemia or hypothermia can impact on analgesic absorption, leading to inadequate analgesia or in late side effects due to the distribution of the medicine depot when perfusion improves [2–4].

Transdermal (TD) Route

The term “transdermal” is used to describe drugs that, when applied to the skin, are systematically absorbed and have predominantly central effects. Fentanyl and buprenorphine, thanks to their lipophilicity, are available as TD preparations, but the onset and offset times of this preparation are slow, and this makes short-term titration impossible. TD fentanyl patches are currently specifically contraindicated for the management of acute or postoperative pain in many countries [59]. Instead, the fentanyl iontophoretic transdermal system has a greater acceptance by nurses and patients than morphine IV PCA [60].

Transmucosal Route

Highly fat-soluble drugs can be administered through a transmucosal route, bypassing first-pass hepatic metabolism and rapidly entering the systemic circulation. Transmucosal routes

include sublingual, buccal, intranasal, and rectal

Rectal Route

Rectal administration can only be used when other routes are not available. Caveats with the rectal route are linked to the variability of absorption and rectal irritation. Contraindications to this route include immune suppression, pre-existing rectal lesions, and recent colorectal surgery.

Both opioids and paracetamol are effective when administered by the rectal route, but the time to peak analgesic effect and the bioavailability can vary widely both between patients and in the same patient.

Rectal opioids play a role primarily in cancer pain management [61].

In children, initial doses of 40 mg/kg of paracetamol followed by 20 mg/kg were found to provide therapeutic blood levels without evidence of accumulation [62].

Rectal NSAIDs demonstrate effective analgesia in many postoperative settings [63]. Local effects such as rectal irritation and diarrhea have been reported, and other commonly reported AEs such as nausea and vomiting have the same incidence in rectal versus other routes. Consequently, there are no advantages in using rectal NSAIDs compared to oral ones.

Intranasal Route (IN)

Absorption through the nasal mucosa is high, and it depends on the lipid solubility and degree of ionization of the drug. The human nasal mucosa contains several metabolizing enzymes, but the clinical consequence of human nasal first-pass metabolism remains unclear. It has been proposed that the volume of a dose of any IN drug should not exceed 150 μ L, in order to avoid run-off into the pharynx.

Several opioids can be effectively administered via the IN route. IN fentanyl has been adopted as treatment for breakthrough cancer pain [64], while no significant difference in postoperative pain relief was found when IN fentanyl was compared to IV morphine, oral morphine, or IV fentanyl [65]. In addition, 3.15 g of IN ketorolac has been shown to be

effective with an opioid-sparing effect after major surgery [66].

IN (6 mg/kg) S-ketamine plus midazolam had similar effects on pain and AEs compared with standard intravenous PCA with morphine in spinal surgery [67].

Sublingual and Buccal Routes

Sublingual (SL) or buccal mucosae are characterized by a large surface for the absorption of drugs, but swallowing can impact their effectiveness.

Many fentanyl preparations are approved for breakthrough cancer pain, either as buccal tablets (FBT) or as a soluble film (FBSF) and orally disintegrating tablet (ODT) of fentanyl citrate. SL preparations are not recommended in opioid-naïve patients or for acute and postoperative pain for the risk of respiratory depression [68].

The bioavailability of SL buprenorphine tablets is about 30–50% with a mean half-life of 28 h. In closed reduction orthopedic surgery, SL buprenorphine (0.4 mg given before induction) can be more efficacious in postoperative pain control than 5 mg of IV morphine [69].

SL sufentanil is available for postoperative pain as a PCA device. It is a preprogrammed tablet delivery system; each dose contains 15 mcg of SL citrate, and patients can self-titrate the dose with a minimum time interval of 20 min. Bioavailability is 59% after a single dose, with a time to C_{max} of 48 min after single dose. In the EU it has been adopted for moderate to severe postoperative pain control as an alternative to IV PCA morphine, with high satisfaction levels [70]. Very few data are available in patients with moderate to severe liver or renal insufficiency; therefore, its use in these particular settings is not recommended.

Epidural Route

Epidural analgesia has become a globally adopted choice for acute pain treatment in surgical settings, above all for labor of childbirth. Epidural analgesia is more efficacious than IV opioid analgesia [1–3, 9, 29]. It is recommended for postoperative pain relief in high-risk

patients (i.e., increased risk of cardiac or pulmonary complications and prolonged ileus) during thoracic, upper abdominal, and lower limb surgery. The quality of epidural analgesia improves with the addition of opioids (4 mcg/mL of fentanyl or 0.5 mcg/mL sufentanil) to local anesthetics (ropivacaine 0.2% or bupivacaine or levobupivacaine at 0.1 or 0.125%). Continuous epidural infusion of opioids and local anesthetics versus IV opioid PCA infusion has been shown to be more effective in pain reduction and less prone to AEs like nausea and vomiting, and to facilitate mobilization [29]. In colorectal surgery, thoracic epidural analgesia (TEA) is associated with a reduced VAS and ileus, without changes in the length of hospital stay and with an increase rate of pruritus, urinary retention, and hypotension compared to systemic opioids [71]. When compared to other pain strategies in open abdominal interventions, TEA ensures better pain relief and bowel function, but does not influence hospitalization stay and complication rates [72].

The rate of cardiac, respiratory, gastrointestinal, and renal complications is lower with TEA compared to lumbar epidural analgesia. In patients with rib fractures, TEA with local anesthetics is associated with a shorter duration of ventilation compared with systemic analgesia [73]. A reduced risk of pain chronification after thoracotomy was found in patients undergoing TEA [74]. In comparison with systemic analgesia, epidural analgesia after cardiac surgery is reported to reduce the incidence of myocardial infarction, ventilatory impairment, and atrial fibrillation/flutter, and the duration of pain and mechanical ventilation after cardiac surgery [75]. Recently, the placement of an epidural catheter under direct vision at the end of complex spine surgical procedures has been recommended, with the use of local anesthetics, combined or not with opioids [76].

Epidural analgesia with local anesthetics can be achieved by continuous infusion or by PCA. Adding clonidine to a local anesthetic could allow for better postoperative pain scores, with an increased number of hypotensive episodes. Its use is not recommended due to the limited evidence [9].

Severe AEs include respiratory depression, severe hypotension, and epidural hematoma or epidural abscess causing paraplegia. Therefore, monitoring patients undergoing neuraxial analgesia is mandatory in order to promptly adopt all appropriate treatments (i.e., catheter removal, dose de-escalation, antagonist administration, decompression surgery, antibiotics).

Intrathecal Route

Intrathecal (IT) local anesthetics provide short-term postoperative analgesia. During orthopedic, urological, and gynecological procedures, the addition of IT morphine (50–100 mcg) allows for longer analgesia than with IT local anesthetics alone [77]. IT opioids seem to better control pain compared to IV administration, even if respiratory depression, urinary retention, nausea, vomiting, and pruritus are more frequent with IT than with IV opioids [78] and if high doses of morphine are used (more than 300 mcg). The rate of AEs is higher during minor surgery than major surgery [79]. No definite conclusion has emerged from literature comparing spinal epidural versus continuous epidural infusion [29]. Combination with clonidine (30–150 mcg) reduces opioid doses, with longer duration [80].

Peripheral Blocks

Regional and local analgesic techniques have been increasingly used for perioperative pain management, and their use is advocated as a part of modern multimodal postoperative analgesia. The introduction of ultrasound-guided procedures has increased the adoption of such techniques, in terms of success rate, time to perform, and onset time [81]. Moreover, ultrasound guidance significantly reduces the risk of local anesthetic systemic toxicity [82] and nerve injury. Recently, specific peripheral approaches have been recommended for some specific surgeries: for example, in major breast surgery, paravertebral block or pectoral nerve block and/or local anesthetic wound infiltration may be considered for additional pain relief [83] or, in cesarean section, continuous wound local

anesthetic infusion, and/or fascial plane blocks such as transversus abdominis plane or quadratus lumborum blocks are recommended [84]. After thoracotomy, thoracic paravertebral block is comparable to TEA, while transversus abdominis plane block is superior to local infiltration for abdominal surgeries, with the exception of laparoscopic cholecystectomy [9].

Nerve trunk blocks are strongly supported for surgeries of the extremities [9].

No differences in time to onset of anesthesia or patient satisfaction were found when comparing levobupivacaine versus ropivacaine for peripheral blocks, with the former providing longer block and a lower incidence of postoperative rescue analgesia. Concentration ranged from 0.5 to 0.75% [85].

Potential risks include nerve injury, bleeding, and infection, and therefore strict adherence to specific guidelines is recommended.

Limitations

The present review deals with the management of acute postoperative pain medications and their different ways of administration, focusing on the most adopted ones. However, several other approaches can be employed to control acute pain and prevent chronification, such as non-pharmacological treatment (i.e., acupuncture), topical treatments and neuroablative/modulatory techniques, like cryo-analgesia [86].

Moreover, other medications should be considered in order to manage pain persistence, such as tricyclic antidepressants, anticonvulsants, or *N*-methyl-*D*-aspartate receptor antagonists. The effective role of all these adjuvants in controlling chronic pain is well known and documented, but their role in acute postoperative pain management needs to be better clarified.

CONCLUSION

One of the most difficult challenges for the pain physician is preventing the persistence of pain after surgical procedures or trauma. An in-depth knowledge of pain mechanisms is fundamental to developing effective pain control strategies,

together with an accurate therapy plan, which very often involves a multimodal approach.

Adding non-pharmacological interventions to analgesic medication may result in additional effects consistent with the biopsychosocial model of pain. For any given situation, a number of potential multimodal combinations are possible, and different multimodal regimens might be appropriate, depending on the specific surgery, individual clinical factors, and patient preferences.

As existing evidence suggests, better knowledge of different routes of administration of analgesics, their indications, and limitations could help pain therapists in providing the most appropriate management of acute pain and preventing the development of chronic pain.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authors' Contributions. MG and FP participated in the conception and design of the paper, GV revised the manuscript, and FP contributed to drafting the manuscript.

Disclosures. Filomena Puntillo and Giustino Varrassi are members of the Editorial Board of *Pain and Therapy*.

Mariateresa Giglio has nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Open Access. This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

- Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, Keefe FJ, Mogil JS, Ringkamp M, Sluka KA, Song XJ, Stevens B, Sullivan MD, Tutelman PR, Ushida T, Vader K. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain*. 2020;161(9):1976–82.
- Chou R, Gordon DB, de Leon-Casasola OA, et al. Guidelines on the management of postoperative pain management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain*. 2016;17(2):131–57.
- Misiołek H, Zajączkowska R, Daszkiewicz A, et al. Consensus statement of the Section of Regional Anaesthesia and Pain Therapy of the Polish Society of Anaesthesiology and Intensive Therapy, the Polish Society of Regional Anaesthesia and Pain Therapy, the Polish Association for the Study of Pain and the National Consultant in Anaesthesiology and Intensive Therapy. *Anaesthesiol Intensive Ther*. 2018;50(3):173–99.
- Aubrun F, Nouette-Gaulain K, Fletcher D, et al. Revision of expert panel's guidelines on postoperative pain management. *Anaesth Crit Care Pain Med*. 2019;38(4):405–11.
- Alam A, Gomes T, Zheng H, Mamdani MM, Juurlink DN, Bell CM. Long-term analgesic use after low-risk surgery: a retrospective cohort study. *Arch Intern Med*. 2012;172(5):425–30.
- McDaid C, Maund E, Rice S, Wright K, Jenkins B, Woolacott N. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for the reduction of morphine-related side effects after major surgery: a systematic review. *Health Technol Assess*. 2010;14(17):1–153.
- Enqvist B, Bjorklund C, Engma M, Jakobsson J. Preoperative hypnosis reduces postoperative vomiting after surgery of the breasts: a prospective, randomized, and blinded study. *Acta Anaesthesiol Scand*. 1997;41:1028–32.
- Weber L, Yeomans DC, Tzabazis A. Opioid-induced hyperalgesia in clinical anesthesia practice: what has remained from theoretical concepts and experimental studies? *Curr Opin Anaesthesiol*. 2017;30(4):458–65.
- Schug SA, Palmer GM, Scott DA, Alcock M, Halliwell R, Mott J. APM: SE Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine, Acute Pain Management: Scientific Evidence (5th edition), ANZCA & FPM, Melbourne. 2020.
- Vallejo R, Barkin RL, Wang V. Pharmacology of opioids in the treatment of chronic pain syndromes. *Pain Physician*. 2011;14:E343–60.
- Plein LM, Rittner HL. Opioids and the immune system—friend or foe. *Br J Pharmacol*. 2018;175(14):2717–25.
- Urman RD, Seger DL, Fiskio JM, et al. The burden of opioid-related adverse drug events on hospitalized previously opioid-free surgical patients. *J Patient Saf*. 2021;17(2):e76–83.
- Hoeben E, Smit JW. Upmalis D et al Dose-response relationship after single oral dose administrations of morphine and oxycodone using laser-evoked potentials on UVB- and capsaicin-irritated skin in healthy male subjects. *Pain*. 2012;153(8):1648–56.
- Derry S, Moore RA, McQuay HJ. Single dose oral codeine, as a single agent, for acute postoperative pain in adults. *Cochrane Database Syst Rev*. 2010;4:CD008099.
- Toms L, Derry S, Moore RA et al Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. *Cochrane Database Syst Rev*. 2009;1:CD001547.

16. Moore RA, McQuay HJ Single-patient data meta-analysis of 3453 postoperative patients: oral tramadol versus placebo, codeine and combination analgesics. *Pain*. 1997;69(3):287–94.
17. McQuay H, Edwards J. Meta-analysis of single dose oral tramadol plus acetaminophen in acute postoperative pain. *Eur J Anaesthesiol Suppl*. 2003;28:19–22.
18. Gaskell H, Derry S, Moore RA, et al. Single dose oral oxycodone and oxycodone plus paracetamol (acetaminophen) for acute postoperative pain in adults. *Cochrane Database Syst Rev*. 2009;3:CD002763.
19. Derry S, Derry CJ, Moore RA. Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults. *Cochrane Database Syst Rev*. 2013;6:CD010289.
20. McCormack JP, Warriner CB, Levine M, et al. A comparison of regularly dosed oral morphine and on-demand intramuscular morphine in the treatment of postsurgical pain. *Can J Anaesth*. 1993;40(9):819–24.
21. Viscusi ER, Allard R, Sohns M, Eerdeken M Tapentadol immediate release for moderate to severe acute post-surgery pain. *J Opioid Manag*. 2019;15(1):51–67.
22. D'Souza RS, Gurrieri C, Johnson RL, Warner N, Wittwer E. Intraoperative methadone administration and postoperative pain control: a systematic review and meta-analysis. *Pain*. 2020;161(2):237–43.
23. Manassero A, Fanelli A, Ugues S, Bailo C, Dalmaso S. Oral prolonged-release oxycodone/naloxone offers equivalent analgesia to intravenous morphine patient-controlled analgesia after total knee replacement A randomized controlled trial. *Minerva Anesthesiol*. 2018;84(9):1016–23.
24. Kokki M, Kuronen M, Naaranlahti T, et al. Opioid-induced bowel dysfunction in patients undergoing spine surgery: comparison of oxycodone and oxycodone-naloxone treatment. *Adv Ther*. 2017;34(1):236–51.
25. Neuman M, Bateman B, Wunsch H. Inappropriate opioid prescription after surgery. *Lancet*. 2019;393:1547–57.
26. Józwiak-Bebenista M, Nowak JZ. Paracetamol: mechanism of action, applications and safety concern. *Acta Pol Pharm*. 2014;71(1):11–23.
27. Bacchi S, Palumbo P, Sponta A, Coppolino MF. Clinical pharmacology of non-steroidal anti-inflammatory drugs: a review. *AntiInflammatory Antiallergy Agents Med Chem*. 2012;11:52–64.
28. Gaskell H, Derry S, Wiffen PJ, Moore RA. Single dose oral ketoprofen or dexketoprofen for acute postoperative pain in adults. *Cochrane Database Syst Rev*. 2017;5:CD007355.
29. Perioperative care in adults. NICE guideline: methods NG180. August 2020.
30. Acharya M, Dunning J. Does the use of non-steroidal anti-inflammatory drugs after cardiac surgery increase the risk of renal failure? *Interact Cardiovasc Thorac Surg*. 2010;11:461–7.
31. Elia N, Lysakowski C, Tramer MR. Does multimodal analgesia with acetaminophen, nonsteroidal anti-inflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. *Anesthesiology*. 2005;103:1296–330.
32. National Clinical Guideline Centre 2011. The management of Hip Fracture in Adults. London. <https://www.ncgc.ac.uk>.
33. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and non-selective inhibitors of cyclooxygenase 2. *JAMA*. 2006;296:1633–44.
34. Nussmeier NA, Whelton AA, Brown MT, Joshi GP, Langford RM, Singla NK, et al. Safety and efficacy of the cyclooxygenase-2 inhibitors parecoxib and valdecoxib after noncardiac surgery. *Anesthesiology*. 2006;104:518–26.
35. Graham DJ, Campen D, Hui R, Spence M, Cheetham C, Levy G, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *Lancet*. 2005;365:475–81.
36. Bellis JR, Pirmohamed M, Nunn AJ, Loke YK, De S, Golder S, Kirkham JJ. Dexamethasone and haemorrhage risk in paediatric tonsillectomy: a systematic review and meta-analysis. *Br J Anaesth*. 2014;113:23–42.
37. Davidson BL, Verheijen S, Lensing AW, Gebel M, Brighton TA, Lyons RM, Rehm J, Prins MH. Bleeding risk of patients with acute venous thromboembolism taking nonsteroidal anti-inflammatory drugs or aspirin. *JAMA Intern Med*. 2014;174:947–53.

38. Modasi A, Pace D, Godwin M, Smith C, Curtis B. NSAID administration post colorectal surgery increases anastomotic leak rate: systematic review/meta-analysis. *Surg Endosc.* 2019;33(3):879–85.
39. Arron MNN, Lier EJ, de Wilt JHW, Stommel MWJ, van Goor H, Ten Broek RPG. Postoperative administration of non-steroidal anti-inflammatory drugs in colorectal cancer surgery does not increase anastomotic leak rate; A systematic review and meta-analysis. *Eur J Surg Oncol.* 2020;46(12):2167–73.
40. EuroSurg Collaborative. Safety and efficacy of non-steroidal anti-inflammatory drugs to reduce ileus after colorectal surgery. *Br J Surg.* 2020;107(2):e161–9.
41. Chincholkar M. Analgesic mechanisms of gabapentinoids and effects in experimental pain models: a narrative review. *Br J Anaesthesia.* 2018;120(6):1315–34.
42. Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg.* 2007;104:1545–56.
43. Verret M, Lauzier F, Zarychanski R, et al. Perioperative use of gabapentinoids for the management of postoperative acute pain a systematic review and meta-analysis. *Anesthesiology.* 2020;133:265–79.
44. Bounes V, Charpentier S, Houze-Cerfon CH, et al. Is there an ideal morphine dose for prehospital treatment of severe acute pain? A randomized, double-blind comparison of 2 doses. *Am J Emerg Med.* 2008;26(2):148–54.
45. Chang AK, Bijur PE, Lupow JB, et al. Randomized clinical trial of the 2 mg hydromorphone bolus protocol versus the “1+1” hydromorphone titration protocol in treatment of acute, severe pain in the first hour of emergency department presentation. *Ann Emerg Med.* 2013;62(4):304–10.
46. Bounes V, Barthelemy R, Diez O, et al. Sufentanil is not superior to morphine for the treatment of acute traumatic pain in an emergency setting: a randomized, double-blind, out-of-hospital trial. *Ann Emerg Med.* 2010;56(5):509–16.
47. Tao B, Liu K, Wang D, Ding M, Zhao P. Effect of intravenous oxycodone versus sufentanil on the incidence of postoperative nausea and vomiting in patients undergoing gynecological laparoscopic surgery. *J Clin Pharmacol.* 2019;59(8):1144–50.
48. Pang WW, Mok MS, Huang S, et al. Intraoperative loading attenuates nausea and vomiting of tramadol patient controlled analgesia. *Can J Anaesth.* 2000;47(10):968–73.
49. Raff M, Belbachir A, El-Tallawy S, Ho KY. Intravenous oxycodone versus other intravenous strong opioids for acute postoperative pain control: a systematic review of randomized controlled trials. *Pain Ther.* 2019;8(1):19–39.
50. Tzortzopoulou A, McNicol ED, Cepeda MS, et al. Single dose intravenous propacetamol or intravenous paracetamol for postoperative pain. *Database Syst Rev.* 2001;10:CD007126.
51. Shi SB, Wang XB, Song JM, Guo SF, Chen ZX, Wang Y. Efficacy of intravenous acetaminophen in multimodal management for pain relief following total knee arthroplasty: a meta-analysis. *J Orthop Surg Res.* 2018;13(1):250.
52. Maxwell EN, Johnson B, Cammilleri J, et al. Intravenous acetaminophen-induced hypotension: a review of the current literature. *Ann Pharmacother.* 2019;53(10):1033–41.
53. De Oliveira Jr. GS, Agarwal D, Benzoni HT. Perioperative single dose ketorolac to prevent postoperative pain: a meta-analysis of randomized trials. *Anesth Analg.* 2012;114(2):424–33.
54. Southworth S, Peters J, Rock A, et al. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen 400 and 800 mg every 6 hours in the management of postoperative pain. *Clin Ther.* 2009;31(9):1922–35.
55. Lloyd R, Derry S, Moore RA, et al. Intravenous or intramuscular parecoxib for acute postoperative pain in adults. *Cochrane Database Syst Rev.* 2009;2:CD004771.
56. Daniels S, Playne R, Stanescu I, Zhang J, Gottlieb I, Atkinson H. Efficacy and safety of an intravenous acetaminophen/ibuprofen fixed-dose combination after bunionectomy: a randomized, double-blind, factorial, placebo-controlled trial. *Clin Ther.* 2019;41(10):1982–95.
57. Hirota K, Lambert DG. Ketamine: new uses for an old drug? *Br J Anaesth.* 2011;107(2):123–6.
58. Brinck EC, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, Kontinen V. Perioperative intravenous ketamine for acute postoperative pain in adults. *Cochrane Database Syst Rev.* 2018;12(12):CD012033.
59. Information for healthcare professionals: fentanyl transdermal system. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm084307.htm>.

60. Pestano CR, Lindley P, Ding L, Danesi H, Jones JB. Meta-Analysis of the Ease of Care From the Nurses' Perspective Comparing Fentanyl Iontophoretic Transdermal System (ITS) Vs Morphine Intravenous Patient-Controlled Analgesia (IV PCA) in Postoperative Pain Management. *J Perianesth Nurs*. 2017;32(4):329–40.
61. Kestenbaum MG, Vilches AO, Messersmith S, et al. Alternative routes to oral opioid administration in palliative care: a review and clinical summary. *Pain Med*. 2014;15(7):1129–53.
62. Gandhi R, Sunder R. Postoperative analgesic efficacy of single high dose and low dose rectal acetaminophen in paediatric ophthalmic surgery. *J Anaesthesiol Clin Pharmacol*. 2012;28(4):460–4.
63. Tramer MR, Williams JE, Carroll D, et al. Comparing analgesic efficacy of non-steroidal anti-inflammatory drugs given by different routes in acute and chronic pain: a qualitative systematic review. *Acta Anaesthesiol Scand*. 1998;42(1):71–9.
64. Zeppetella G, Davies AN. Opioids for the management of breakthrough pain in cancer patients. 201. *Database Syst Rev*. 2013;10: CD004311.
65. Hansen MS, Mathiesen O, Trautner S, Dahl JB. Intranasal fentanyl in the treatment of acute pain—a systematic review. *Acta Anaesthesiol Scand*. 2012;56(4):407–19.
66. Garnock-Jones KP. Intranasal ketorolac: for short-term pain management. *Clin Drug Investig*. 2012;32(6):361–71.
67. Riediger C, Haschke M, Bitter C, Fabbro T, Schaeren S, Urwyler A, Ruppen W. The analgesic effect of combined treatment with intranasal S-ketamine and intranasal midazolam compared with morphine patient-controlled analgesia in spinal surgery patients: a pilot study. *J Pain Res*. 2015;13(8):87–94.
68. FDA. Medication Guide ACTIQ® (fentanyl citrate) oral transmucosal lozenge. 2011. <http://www.fda.gov/downloads/drugs/drugsafety/ucm085817.pdf>.
69. Soltani G, Khorsand M, Shamloo AS, Jarahi L, Zirak N. Comparison of Intravenous Morphine with Sublingual Buprenorphine in Management of Postoperative Pain after Closed Reduction Orthopedic Surgery. *Arch Bone Jt Surg*. 2015;3(4):280–5.
70. Frampton JE. Sublingual Sufentanil: a review in acute postoperative pain. *Drugs*. 2016;76:719–29.
71. Shi WZ, Miao YL, Yakoob MY, et al. Recovery of gastrointestinal function with thoracic epidural vs. systemic analgesia following gastrointestinal surgery. *Acta Anaesthesiol Scand*. 2014;58(8):923–32.
72. Hughes MJ, Ventham NT, McNally S, et al. Analgesia after open abdominal surgery in the setting of enhanced recovery surgery: a systematic review and meta-analysis. *JAMA Surg*. 2014;149(12):1224–30.
73. Carrier FM, Turgeon AF, Nicole PC, et al. Effect of epidural analgesia in patients with traumatic rib fractures: a systematic review and meta-analysis of randomized controlled trials. *Can J Anaesth*. 2009;56(3):230–42.
74. Andreae MH, Andreae DA. Local anaesthetics and regional anaesthesia for preventing chronic pain after surgery. *Cochrane Database Syst Rev*. 2012;10: CD007105.
75. Guay J, Kopp S. Epidural analgesia for adults undergoing cardiac surgery with or without cardiopulmonary bypass. *Cochrane Database Syst Rev*. 2019;1(3):CD006715.
76. Waelkens P, Alsabbagh E, Sauter A, Joshi GP, Beloeil H. On behalf of the PROSPECT Working Group* of the European Society of Regional Anaesthesia and Pain Therapy (ESRA) Pain management after complex spine surgery: A systematic review and procedure-specific postoperative pain management recommendations. *Eur J Anaesthesiol*. 2021;37: 1–10.
77. Popping D, Elia N, Marret E, et al. Opioids added to local anesthetics for single-shot intrathecal anesthesia in patients undergoing minor surgery: a meta-analysis of randomised trials. *Pain*. 2012;153: 784–93.
78. Wang J, Sun H, Sun WT, Sun HP, Tian T, Sun J. Efficacy and safety of intrathecal morphine for pain control after spinal surgery: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci*. 2021;25(6):2674–84.
79. Meylan N, Elia N, Lysakowski C, et al. Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials. *Br J Anaesth*. 2009;102(2):156–67.
80. Engelman E, Marsala C. Efficacy of adding clonidine to intrathecal morphine in acute postoperative pain: meta-analysis. *Br J Anaesth*. 2013;110(1):21–7.
81. Abrahams MS, Aziz MF, Fu RF et al. Ultrasound guidance compared with electrical neurostimulation for peripheral nerve block: a systematic review and meta-analysis of randomized controlled trials. *Br J Anaesth*. 2009;102(3):408–17.
82. Melnyk V, Ibinson JW, Kentor ML, et al. Updated retrospective single-center comparative analysis of peripheral nerve block complications using landmark peripheral nerve stimulation versus

- ultrasound guidance as a primary means of nerve localization. *J Ultrasound Med.* 2018;37(11):2477–88.
83. Jacobs A, Lemoine A, Joshi GP, Van de Velde M, Bonnet F on behalf of the PROSPECT Working Group collaborators. PROSPECT guideline for oncological breast surgery: a systematic review and procedure-specific postoperative pain management recommendations. *Anaesthesia.* 2020;75(5):664–73.
84. Roofthoof E, Joshi GP, Rawal N, Van de Velde M. PROSPECT Working Group* of the European Society of Regional Anaesthesia and Pain Therapy and supported by the Obstetric Anaesthetists' Association. PROSPECT guideline for elective caesarean section: updated systematic review and procedure-specific postoperative pain management recommendations. *Anaesthesia.* 2021;76(5):665–80.
85. Li A, Wei Z, Liu Y, et al. Ropivacaine versus levobupivacaine in peripheral nerve block: A PRISMA-compliant meta-analysis of randomized controlled trials. *Medicine (Baltimore).* 2017;96(14): e6551.
86. Mihalko WM, Kerkhof AL, Ford MC, Crockarell JR Jr, Harkess JW, Guyton JL. Cryoneurolysis before Total Knee Arthroplasty in Patients with Severe Osteoarthritis for Reduction of Postoperative Pain and Opioid Use in a Single-Center Randomized Controlled Trial. *J Arthroplasty.* 2021;36(5):1590–8.