Pharmacological Research 65 (2012) 411–429

Contents lists available at SciVerse ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Non-opioid IV adjuvants in the perioperative period: Pharmacological and clinical aspects of ketamine and gabapentinoids

Avi A. Weinbroum*

Post Anesthesia Care Unit, Tel Aviv Sourasky Medical Center, Tel Aviv, the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ARTICLE INFO

Article history:
Received 29 November 2011
Received in revised form 4 January 2012
Accepted 4 January 2012

Keywords:
Adjuvants
Non-opioids
Analgesia
Pharmacology
Ketamine
Gabapentinoids

ABSTRACT

Untreated acute postoperative pain can transform into chronic pain that may have major negative effects on the individual's quality of life. It can also prolong recovery, rehabilitation and length of hospital stay, thus affecting societal economic burden. Given the multiplicity of mechanisms involved in postoperative pain, a multimodal analgesia regimen, using a combination of opioids and multiple agents aiming to augment their effects via different routes of administration, is a pharmacologically appropriate approach. This polypharmacological application provides superior pain relief at rest and after movement, reduced opioid consumption associated with reduced analgesic-related adverse effects, and better chances to prevent the induction of later hyperalgesia. The most important adjuncts currently employed are ketamine and gabapentinoids. They have been shown to help in reaching the desired effect when administered at drug-specific modes and at proven effective dosing throughout the perioperative period.

Contents

Abbreviations: b.i.d., twice daily; BIS, bispectral; CABG, coronary artery bypass grafting; CRP, C-reactive protein; CSF, cerebrospinal fluid; GA, general anesthesia; GBP, gabapentin; IV, intravenous; NRS, numerical rating scale; LPS, lipopolysaccharide; NSAIDs, non-steroidal anti-inflammatory drugs; PACU, post-anesthesia care unit; PCA, patient-controlled analgesia; PGL, pregabalin; POD, postoperative day; PONV, postoperative nausea and/or vomiting; RCT, randomized control trial; t.i.c., trice daily; TNF-α, tumor necrosis factor-alpha; TNF RI, tumor necrosis factor-alpha receptor 1; VAS, visual analogue scale; WCP, wound care procedure.

* Correspondence address: Post-Anesthesia Care Unit & Pre-Clinical Research Laboratory, Tel Aviv Sourasky Medical Center, 6 Weizman St., Tel Aviv 64239, Israel. Tel.: +972 3 6973237; fax: +972 3 6925749.
E-mail address: draviw@tasmc.heatlh.gov.il

1043-6618/$ – see front matter © 2012 Published by Elsevier Ltd.
doi:10.1016/j.phrs.2012.01.002

1. Part I: ketamine

1.1. Introduction

Early postoperative pain is the most common complaint in the recovery room, even after laparoscopic surgery [1]. Postoperative pain is the primary reason for prolonged convalescence [2] and one of the main concerns of the surgical patient. Data suggest that pain may be inadequately treated in ~50% of all surgical procedures [3]. In addition to providing analgesia and minimizing patient suffering, the objectives of proper treatment of pain are preventing or attenuating the central neural hyper-excitability that increases postoperative pain [4,5], reducing to minimum the transformation of acute pain into chronic pain [6], and the built-up of analgesic tolerance or hyperalgesia [7]. Given the multiplicity of mechanisms involved in postoperative pain (Fig. 1) [8], an appropriate approach would be a multimodal analgesia regimen that uses a combination of opioids and multiple agents (e.g., local anesthetics, non-steroidal anti-inflammatory drugs [NSAIDs], paracetamol, ketamine, α_2-adrenoreceptor agonists), aiming at augmenting their reciprocal effects [6–9]. This application provides superior pain relief at rest and after movement, as well as reduced opioid consumption and analgesic-related adverse effects, e.g., respiratory depression, hypotension, sedation, nausea, vomiting, constipation, urinary retention [10–12]. Adjuncts are typically administered at regular dosing intervals for several days throughout the perioperative period. One of the developments that have driven research to better understand pain pathophysiology and optimally use analgesics in this direction is the shift of ever-larger volumes of interventions to office or outpatient surgery suites. The effectiveness of multimodal analgesia has, however, been only partially implemented into regular and adequate clinical practice [13,14].

Postoperative pain may initiate prolonged changes in both the peripheral and the central nervous system that lead to the

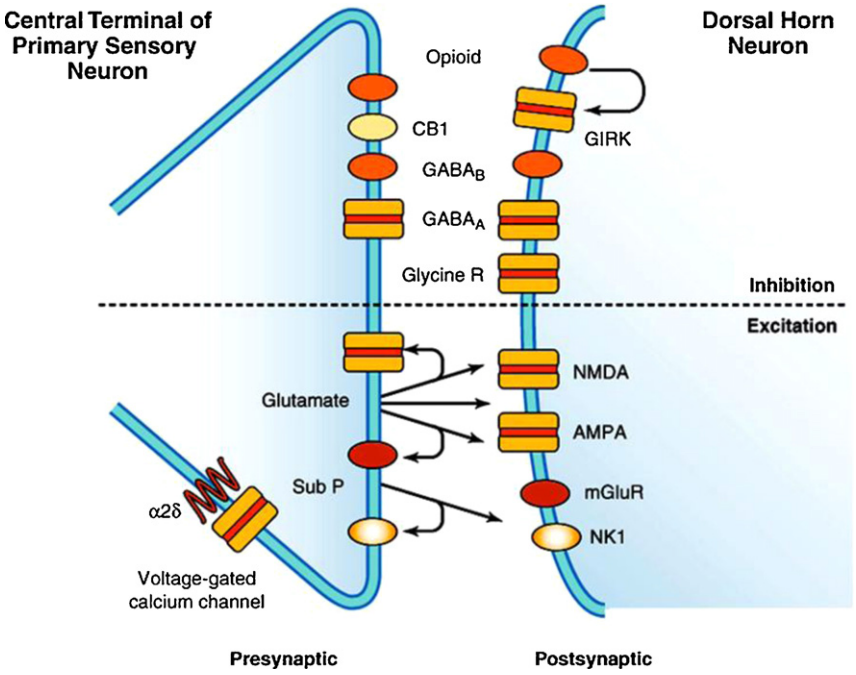

Fig. 1. Neurophysiological mechanisms involved in pain stimulations/control.
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amplification and prolongation of pain. Peripheral and central sensitizations contribute to the postoperative hypersensitivity state that is responsible for a decrease in pain threshold and for the establishment of aberrant excitatory synaptic connections, both at the site of injury (primary hyperalgesia) and in the surrounding uninjured tissue (secondary hyperalgesia) [15]. Because of their role in peripheral and central sensitization, both ketamine and gabapentinoids have sparked interest as part of a preventive multimodal analgesic modality that may be used for either protective premedication or preventive analgesia. *Preemptive treatment* involves the use of adjuvants, sometimes alone but mostly in combination with opioids, administered before the onset of pain. Effective *preventive analgesia* results when drugs are administered immediately after injury has been afflicted [16], and pain has been induced [17]. Both measures result in reduced postoperative pain and a decrease in the incidence or severity of persistent post-surgical pain.

Two classes of drugs are currently an essential part of the multimodal analgesia protocols (Fig. 1):

I. Intravenous (IV) *ketamine*, a phencyclidine derivative
II. Oral *gabapentin* (GBP) and *pregabalin* (PGL), both gabapentinoids.

This article will review the neuropharmacological characteristics of these drugs, the modes of usage and will guide the reader in achieving greatest clinical benefits from their added pharmacological values.

2. Pharmacology

Ketamine affects multiple receptors: the N-methyl-D-aspartate receptor (NMDAR) is the main one, and opioid receptors and monoaminergic receptors are involved as well [18]. In high doses, ketamine also affects sigma opioid receptors, block muscarinic cholinergic receptors, and potentiates GABAergic neurotransmission. Animal studies have also identified NMDA-glutamate receptors on peripheral nerves [19]. Systemically administered ketamine has local anesthetic action, and spinal effects have been documented [20] but that route is seldom used clinically. Ketamine has recently been shown to inhibit tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) gene expressions in lipopolysaccharide (LPS)-activated macrophages [21]. It has been speculated that these anti-proinflammatory effects may be responsible for the anti-hyperalgesic effects of ketamine [22]. Indeed, subanesthetic [see below] S-(+)-ketamine bolii followed by infusion was shown to reduce cardiopulmonary bypass-associated pro-inflammatory cytokine release [23].

There are the two commercially available pharmacological forms of ketamine. One is the racemic presentation (R-ketamine), and the other is the S-(+)-ketamine. Esketamine or (S)-ketamine (brand: Ketanest S) is the (S)-enantiomer of ketamine, which is the more active (3–4 times) constituent chirality out of the dual (R/S) mixed/racemic chiral variety, in which ketamine is most often prepared and induces fewer adverse effects than the R-ketamine [24]. Thus, unless otherwise specified, the racemic ketamine is the form used in cited studies.

2.1. NMDAR

Ketamine binds preferentially to the NMDAR on inhibitory interneurons. It inhibits NMDAR-mediated glutamatergic inputs to GABAergic interneurons, leading to aberrant excitatory activity in the cortex, hippocampus, and limbic system and ultimately unconsciousness. In the spinal cord, ketamine decreases arousal by blocking NMDAR glutamate (Glu)-mediated nociceptive signals from peripheral afferent neurons in the dorsal-root ganglion to projecting neurons. The potent anti-nociceptive effects of ketamine on NMDAR in the spinal cord and its inhibition of acetylcholine release from the pons also contribute to unconsciousness [25]. Hallucinations may result because the aberrant activation allows the association of information in a manner that is inconsistent in time and space.

2.1.1. Relevance

The underlying pharmacology of ketamine is fundamentally different from that of other procedural sedation and analgesia agents. It exerts its effects by “disconnecting” the thalamo-cortical and

limbic systems, i.e., dissociating the central nervous system from outside stimuli, allowing for complete analgesia as well.

Ketamine is a molecule, which contains a chiral carbon atom. During inflammation or nociceptive stimuli, there is increased glutamate and aspartate release in the spinal dorsal horn, and increased synthesis of neurokinins in sensory ganglion cells. These compounds mediate the central sensitization and facilitate the wind-up process. The receptor is not activated when the Ca^{2+} channels at the NMDAR are blocked by ketamine. As a result, no signaling that would otherwise be activated when nociceptive stimuli arrive either at the site or in the presence of excitatory amino acid (e.g., glutamate) will traverse upwards and thus block pain sensation.

Among the potential mechanisms leading to opioid-induced hyperalgesia and anti-nociceptive tolerance, the NMDAR plays a key role in facilitating the process [26,27]. This suggests that preventive administration of clinically available NMDAR antagonists before opiate compound administration during surgical procedures may not only prevent central sensitization induced by tonic nociceptive inputs associated with surgical lesions [28], but also prevent long-lasting enhancement in pain sensitivity induced by the opiate treatment per se [29]. It has also been reported that NMDAR antagonists prevent opiate-induced hyperalgesia [29–34]. All these lines of evidence suggest that employing ketamine to achieve "balanced analgesia" could represent an optimal strategy to prevent pain sensitization induced by both nociceptive inputs and opiates.

3. Metabolism

Ketamine is metabolized in the liver with an elimination half-life of 180 min. The two main metabolites, norketamine and hydroxynorketamine, are both active, and analgesia will persist after awakening [35]. These features enable ketamine to be effective in subanesthetic doses. The metabolism of ketamine involves the activity of multiple enzymes [36]. Long-term, low-dose infusions of ketamine in the intensive care unit (ICU) were not associated with drug accumulation in patients with acute renal failure [37], and its uneventful use has been documented in a hemodialysis-dependent patient as well [38].

4. Physiology and untoward effects

The central respiratory drive depression is minimal; upper airway muscle, pharyngeal, and laryngeal reflexes are preserved; and there is a bronchodilator effect; minute volume is slightly and transiently decreased. Importantly, protective reflexes, such as the pharyngeal, laryngeal, eyelid, and the corneal, are active under the effects of ketamine.

In a study in rats [39] it was found that ketamine increases genioglossus muscle activity while abolishing the coupling between loss of consciousness and upper airway dilator muscle activity. This implies that the contraction of the large genioglossus muscle would elevate human tongue and push it forward, increasing the diameter of the upper airway and decreasing its collapsibility [40]. Thus, unlike other general anesthetics that cause hypotonia and subsequent posterior displacement to a position where the tongue may occlude the pharynx, ketamine preserves upper and lower airway patency.

Most of the untoward effects are associated with high IV bolus doses of ketamine (i.e., >1.5 mg/kg). Although ketamine produces dissociative anesthesia with profound analgesia, airway tone, and reflexes are maintained. Aspiration during the use of ketamine has been recorded, but the drug promotes gut motility, so that vomiting after its administration is unusual. Ketamine produces a sympathomimetic effect due to brain stem stimulation, which leads to catecholamine release and an inhibition of noradrenalin reuptake. Therefore, it increases the pulse rate and stroke volume, leading to an increase in the mean blood pressure. The patient therefore continues to breathe spontaneously and blood pressure is normal or increased [41]. Several pediatric studies showed that airway and respiratory adverse events occur in 1.4–6.6% of the patients and laryngospasm in 0.4% [42,43]. Hypersalivation may occur and is more commonly detected in children than adults [42–44].

One large-scale (>8000 children) review of ~50% ED orthopedic cases [44] showed that IV doses of ketamine >2.5 mg/kg or a total dose >5.0 mg/kg increased the risk of airway and respiratory adverse events by several folds, primarily through an increase in apnea rate. Lower IV loading doses (~1.5 mg/kg) produced satisfactory dissociation and procedural conditions that were as effective as larger doses. The high rate of adverse events in that study occurred more frequently in children who were >2 < 14 years of age, and where high total ketamine cumulative effects was evident. Such laryngospasm seems to be idiosyncratic, and accordingly, clinicians administering ketamine must be prepared for its rapid identification and management: supplemental oxygen and positive-pressure ventilation. If these are unsuccessful and the situation is dire, skeletal muscle relaxation and endotracheal intubation are indicated; co-administration of anticholinergics is unnecessary.

Another review of >4000 patients sedated with ketamine in the emergency department (ED) demonstrated that the odds of a severe adverse event was >2-fold higher when ketamine was administered intramuscularly (IM): the risk of laryngospasm was >5-fold higher than after IV treatment [45].

Patients given anesthetic doses of ketamine (see below) have a typical catatonic appearance. They are unconscious and amnesic, but their eyes usually remain open and exhibit nystagmus. It is wise to warn the staff and family members that this is normal and that the patient is amnesic and unaware of his/her surroundings. Despite the reassuring results of a meta-analysis [46], clinical studies [2,33,34,47] and reviews [48,49], the possibility of excessive sedation or the appearance of psychedelic events – mostly following a full anesthetic IV dose – may still deter its use, by some clinicians.

There was no respiratory depression or need for any intervention to maintain patent airways reported in a prospective study on sedation for fracture manipulation in the ED, in which a regimen of ketamine + propofol (maximal dose of each 0.75 mg/kg) was compared to propofol alone (target dose 0.5–1.5 mg/kg) [50]. However, three propofol + ketamine patients reported experiencing unusual, vivid or "realistic" dreams while sedated. In another prospective study on 92 ED adults [51], adequate sedation and successful completion of the procedure were obtained in 91 patients that received 0.5–1.0 mg/kg ketamine alone. Adverse events occurred in 20 patients, none requiring treatment. Twelve patients recovered in a state of agitation, seven of whom required midazolam IV. One patient experienced agitation + vomiting during recovery and one vomited and hypersalivated. There were no laryngospastic events.

4.1. Pharmacological–clinical relevance

Ketamine's neuro-pharmacological characteristics increases muscle tone, including the upper airways. Laryngospasm may occur, however, following high dose injection (see below).

4.2. Genetic reservations

Finally, ketamine has recently been linked with neonatal rat brain cell apoptosis: the implication in humans has not yet been determined [52].

5. Clinical application

The dose ranges of ketamine have changed over the five decades since its first clinical use. Originally, it was given at the dose of

0.5–1 mg/lb body weight. The subsequently recommended anesthetic dose was 1–2 mg/kg IV [53], or 3–5 mg/kg if administered IM, and a ~50% reduction was suggested if sedation was the desired clinical end-point. Because of its side effects, the recommended dose has recently been further reduced to boluses of <1 mg/kg administered IV (or epidurally) or an infusion rate of <20 μg/kg/min (~1.2 mg/kg/h) [54,55]. During the last decade, the clinical applicable dose was decreased even further, and is now labeled as being a "subanesthetic dose" where the IV bolus dose is ≤0.5 mg/kg and the infusion rate is <0.5 mg/kg/h [56]. Our group has demonstrated that even smaller IV doses (≤250 μg/kg) effectively controlled opioid-resistant pain, although it was associated with a brief period of sedation (<2 min) immediately after the IV injection, but with no psychomimetic events [47]. The usefulness of IV ketamine subanesthetic boluses (doses as low as ≥100 μg/kg) given after opioid administration, were proven effective for analgesia when used by the London's air ambulance [57] and in patients undergoing orthopedic and general surgical interventions [31–34,58,59]. Ketamine combined with opioids potentiates analgesia, thus reducing the need for large opioid doses [34,60]. It has been estimated that pain is reduced by 20–45% [6,34,47]. At the above currently employed clinical doses, ketamine given alone and with no previous opioid administration does not seem to beneficially modulate long-term pain [61,62]. Such lack of pharmacological success may be attributed to an insufficient effective ketamine dose, changes in its pharmacokinetics or dynamics, or type of surgery and less than effective doses of anesthetic drugs used perioperatively.

The data of ketamine use available in the literature has led to conclude that it can reduce postoperative pain intensity, based on Level A evidence (=at least 2 level I [=Level I study is a large RCT with clear results, low risk of false positive {alpha} or false negative {beta} errors studies]). The incidence of its benefit in reducing postoperative nausea and vomiting (PONV) has been confirmed by Level B evidence (=1 study level I), and the effect on lowering the required dose of morphine by 30–50% by Level A evidence [63].

The following data aim at helping the clinician, who plans to use ketamine, in assessing its pharmacological benefits based on various aspects:

(1) location of administration (e.g., pre- or intra-hospital administration);
(2) time of administration (e.g., pre-incisionally or postoperatively);
(3) when adapted for specific types of interventions (e.g., orthopedics versus general surgery).

6. Modes of administration

6.1. Location of administration

6.1.1. Pre-hospital

Pain relief is an essential component of pre-hospital care [64], and ~80% of patients with extremity fractures will suffer moderate to severe pain after having suffered bone fracture [65]. Compared to powerful analgesics that are associated with clinically relevant complications [66], ketamine offers effective analgesia under safe conditions, since it avoids the potential decrease in blood pressure and respiratory depression, both of which are associated with opioid analgesia [57,67,68]. Oxygen desaturation or minimal airway loss may occur after ketamine administration; however, they seem unrelated to the drug, and were never critical, and did not necessitate emergent interventions [57]. When administered on site, IV morphine sulphate 0.1 mg/kg combined with 0.2 mg/kg ketamine top-ups resulted in ~50% lower numerical rating scale (NRS) and a similar magnitude of morphine-sparing effect upon arrival to the ED, compared to morphine alone (0.2 mg/kg) [69]. Intranasal S-ketamine (0.2 mg/kg) was advocated in conditions in which parenteral access is impossible [70]; however, there are some concerns regarding administration via this route [71,72], mainly due to an eventual high plasma concentration built-up, and high variability of effects.

In 30 cases of predicted or unpredicted difficult airway, fentanyl IV 3–4 μg/kg + ketamine 0.6–0.7 mg/kg subcutaneously + lidocaine spray 4% locally enabled first try secure awake intubation without oxygen desaturation or other untoward events [73].

6.1.1.1. Pharmacological–clinical relevance. (1) IV ketamine alone or in combination with an opioid is a useful pharmacological approach for pre-hospital analgesia provision in trauma patients and for wound care; (2) it is helpful when intubation is of possible difficulty; (3) ketamine seems to be the best drug for rapid sequence induction in hemodynamically compromised [74], or in trauma patients.

6.1.2. Emergency department

We use ketamine frequently as an ideal procedural drug for patients in the ED. Due to its neuropharmacological aspects, it is easily titrated, rapid in onset, relatively brief in duration, and provides sedation and analgesia without respiratory or hemodynamic compromise [unpublished data]. Some disagree [50], mainly with regard to the occasional prolonged time to full awakening and the mandatory need for escort at discharge [75]. Dallimore et al. [76] evaluated racemic ketamine for sedation for painful procedures in 2–12-year-old children. Small repeated boluses (0.275–0.35 mg/kg) followed by infusion (2.5–3.5 mg/kg/h) resulted in fast recovery (20 min).

Ketamine at ~0.5 mg/kg was compared to propofol 1 mg/kg IV, both followed by ketamine 0.5 mg/kg top-ups every 3 min in adults in the ED. More ketamine patients experienced subclinical respiratory depression, without the need for intervention. Amnesia and analgesia rates were equal, but recovery agitation in the ketamine patients was 4-fold that in the propofol + ketamine patients. The median recovery time of the ketamine agitated individuals was 20 min (range 2–45) compared to 8 min (range 1–47) in the propofol + ketamine individuals [77].

A 28-adult study on procedural sedation for fracture manipulation in a Level 1 trauma center ED, compared propofol (target dose 0.5–1.5 mg/kg) and propofol + ketamine (ketofol, administered at a target dose of 0.75 mg/kg). There was a small decline in systolic blood pressure, a better bispectral index (BIS) score, and ~40% lower mean propofol use in the ketamine + propofol patients compared to the propofol alone patients [50].

6.1.2.1. Pharmacological–clinical relevance. IV ketamine is an effective agent for procedural sedation and analgesia in the adult and pediatric populations in the ED, when given alone at a low dose (0.1–0.6 mg/kg) [78] or as ketofol.

6.1.3. ICU

From the sparse available data, it appears that it is safe to use ketamine both as an anesthetic and as an adjuvant for multimodal analgesia in the ICU. This is true even for patients with damage to the central nervous system [79]. Care must be taken, however, to maintain normocapnea. One study showed that long-term, low-dose infusion of ketamine in the ICU was not associated with drug accumulation in patients with acute renal failure [37].

6.2. Perioperative administration: timing and purposes

6.2.1. Preoperatively, for pre-emptive analgesia

The advantageous effects of preoperative opiate administration, i.e., preemptive analgesia, is well acknowledged [80,81], but it may contribute to "preempt hyperalgesia", not analgesia [82]. NMDAR antagonists prevent and reduce the development of pain sensitization, especially if opiate-induced. In their review, Schmid et al. reported a number of studies that detected preemptive effects of low doses of ketamine, i.e., <1 mg/kg IV, epidurally, or ≤20 μg/kg/min IV, although its analgesic effect per se is questionable when administered at inappropriate time or dose [54].

A recent study by our group has demonstrated that ketamine alone administered 4–18 h preoperatively reduced postoperative pain by 30–45% and provided a similar level of morphine-sparing effects: it did not, however, produce any analgesic effect pre-incisionally [61].

6.2.1.1. Pharmacological–clinical relevance. Pre-incisional ketamine at subanesthetic dose (bolus alone or bolus + infusion) is preempts pain and opioid consumption (see Section 6.2.2 and below).

6.2.2. Intraoperatively, for preventive analgesia and anti-hyperalgesia

The vast majority of the studies in the literature report the use of ketamine intraoperatively. Preventative analgesia by intraoperative ketamine was summarized in two reviews [83,84]. The drug generates a median of 33% reduction in acute postoperative opioid consumption and 20–25% pain reduction up to 48 h after surgery [34]. There are several reports on the use of ketamine during different time periods. Joly et al. [85] studied intraoperative remifentanil low (0.05 μg/kg/min) versus high (0.4 μg/kg/min) dose, compared with remifentanil high dose + 0.5 mg/kg ketamine, starting after the induction, and followed by an intraoperative infusion of 5 μg/kg/min until skin closure, and then 2 μg/kg/min for 48 h. The level of hyperalgesia and allodynia (von Frey hair stimulation) and morphine requirements were all greater in the high remifentanil group compared to the low dose and the remifentanil + ketamine group.

6.2.2.1. Pharmacological–clinical relevance. Ketamine is pharmacologically effective in abolishing remifentanil-induced lasting hyperalgesia.

In contrast [86], less intraoperative remifentanil was needed when abdominal surgery under remifentanil-desflurane-based anesthesia was supplemented with intraoperative ketamine 0.15 mg/kg + 2 μg/kg/min infusion, and 0.15 mg/kg morphine. Pain scores were lower only during the first 15 postoperative minutes.

6.2.2.2. Relevance. The additive effect of remifentanil and desflurane may potentiate hyperalgesia in the presence of low ketamine dose which then would not attenuate it. Nevertheless, 33% less morphine was still used with ketamine.

Forty-nine patients undergoing open thoracotomy were treated with continuous epidural infusion of ropivacaine and IV ketamine 0.05 mg/kg/h (~3 mg/h) [87]. Epidural analgesia and ketamine were administered for 2–3 days. The pain visual analogue scores (VAS) at rest and on coughing at 24 and 48 h postoperatively and NRS scores for baseline pain at 1 and 3 months after surgery were lower with ketamine.

In a second report by the same group, 100 patients undergoing surgery for rectal adenocarcinoma under combined epidural (bupivacaine + sufentanil + clonidine mixture)/balanced GA [88] received saline, or ketamine 0.25 mg/kg IV bolus + 0.125 mg/kg/h infusion, 0.5 mg/kg IV + 0.25 mg/kg/h, 0.25 mg/kg epidural bolus of ketamine + 0.125 mg/kg/h infusion, or 0.5 mg/kg epidural bolus + 0.25 mg/kg/h infusion. All the IV and epidural analgesics were stopped at the end of surgery and patients were connected to morphine-PCA. The extent of hyperalgesia and morphine requirements were best reduced in the 0.5 mg/kg IV + 0.25 mg/kg/h group, where the lowest residual pain was reported 6 months later.

The usefulness of ketamine as a local anesthesia adjuvant is also of pharmaco-clinical interest. For example, Tverskoy et al. [89] demonstrated that bupivacaine (0.5%) + ketamine (0.35%) afforded better analgesia compared to bupivacaine alone in cases of wound infiltration after herniorrhaphy.

6.2.2.3. Pharmacological–clinical relevance. Intraoperative ketamine 0.5 mg/kg IV + 0.25 mg/kg/h reduce optimally postoperative hyperalgesia following low abdominal surgery under GA + RA. Systemic administration of ketamine is the preferred one, although its local effects are of clinical use.

6.2.3. Postoperatively, for preventive analgesia and anti-hyperalgesia

Postoperative ketamine administration by boluses, infusion or both, or perioperative (pre-incisional and intraoperative) administration are frequent modes of usage. Postoperative administration is typical via PCA. Some physicians favor infusion, reasoning that ketamine mixed with morphine via PCA is less effective than a continuous infusion because the pharmacokinetic and dynamic effects in the former could be suboptimal. Our group found that PCA-delivered morphine + ketamine was consistently highly effective (see Sections 7.5 and 9).

Based on six a 330 patients cohort, one review [90] concluded that ketamine infusion decrease IV and epidural opioid requirements in six out of 11 studies; a single bolus dose decreased them in seven of 11 studies. Five out of eight trials with epidural ketamine showed beneficial effects as well. Another review [49] summarized the use of ketamine in addition to PCA-morphine (284 patients) following surgical procedures. Three of five studies demonstrated a decrease in postoperative pain intensity.

A more recent Cochrane review [46] analyzed 37 studies (2240 patients) and found that subanesthetic ketamine doses were effective in reducing 24-h morphine requirements and the incidence of PONV; the adverse effects were mild or absent.

6.2.3.1. Pharmacological–clinical relevance. Conflicting findings regarding the pharmacological coadjuvating effects of ketamine exist in the literature. They stem from methodological and patient heterogeneity, variability in the PCA device protocols, mode of ketamine administration, dose, the severity of pain at ketamine initiation, and/or the method of pain measurement. Noteworthy, an application of postoperative combination of PCA-ketamine + morphine has been proven beneficial by the author and his group of researchers (see Sections 7.5 and 9) [2,31–34,47]. Overall, intra- and postoperative ketamine at very low doses (subanesthetic doses, e.g., 0.25–0.5 mg/kg) + infusion, or combined with PCA-morphine, attenuates postoperative pain in most cases, and minimize long-term hyperalgesia. Ketamine also aids in sparing consumption of morphine and other antinociceptives.

7. Ketamine for surgical subspecialties

7.1. Orthopedics

The postoperative course of this type of surgery is characteristically very painful. Recent literature has revealed that ketamine administration leads to opioid-sparing effects after knee arthroscopy [58], anterior cruciate ligament repair [59], knee arthroplasty [91,92], oncologic orthopedic surgery [34], lumbar

disk surgery [93], and cervical spine surgery [94]. This is independent of pain reduction.

7.1.1. Knee arthroscopy

Standard GA + bupivacaine (0.5%) + morphine 5 mg that were injected intra-articularly + IV ketamine (0.15 mg/kg), or placebo, was studied. Ketamine group had less pain at rest and during mobilization on POD 0–2 compared to placebo. Oral acetaminophen + dextropropoxyphene was less required as well [58].

7.1.2. Knee arthroplasty

Remifentanil-based GA, combined with ketamine 120 μg/kg/h during surgery and 60 μg/kg/h for the first two PODs, resulted in reduced postoperative morphine consumption, and pain scores at rest and on mobilization compared to nefopam 0.2 mg/kg bolus or placebo. Knee flexion improved by 20% by both nefopan and ketamine compared to the saline group, and the time to full 90° knee flexion was reduced by 30% [91].

In a similar type of surgery under GA combined with continuous femoral nerve block (0.3 ml/kg 0.75% ropivacaine + 0.2% at 0.1 ml/kg/h/48 h, starting before surgery), patients received 0.5 mg/kg ketamine followed by 3 μg/kg/min during surgery and 1.5 μg/kg/min/48 h or saline. The ketamine patients consumed less PCA-morphine than the saline group and actively flexed their operated knees to 90° in half the time. However, the outcomes at 6 weeks and 3 months were similar [92].

7.1.3. Hip replacement

Remérand et al. [95] studied 150 patients undergoing primary non-oncologic total hip arthroplasty under GA + IV ketamine 0.5 mg/kg before incision + 2 μg/kg/min/24 h. This low-dose ketamine infusion favored the decrease of residual pain at rest by 67% at 6 months after surgery.

A review by Tang et al. illustrates various protocols of multimodal pain treatment used for hip replacement [96].

7.1.3.1. Pharmacological–clinical relevance. Ketamine pharmacologically potentiates opioids when used peri-interventionally on articulations. It induces an optimal opioid-sparing effect, decreases pain intensity, and improves mobilization even after total knee and hip replacements. Late anti-hyperalgesic effects following these procedures, however, are not yet proven.

7.1.4. Anterior cruciate ligament repair

Patients undergoing anterior cruciate ligament (ACL) repair who received IV ketamine 0.15 mg/kg bolus either before surgical incision or at the end of surgery had better results compared to saline [59]: both ketamine groups used less morphine than the saline group over the 48 postoperative hours. They also performed first knee flexion using less morphine. Interestingly, the 24–48-h-morphine demand was higher in the pre-surgery ketamine group than in the post-surgery ketamine group.

7.1.4.1. Pharmacological–clinical relevance. Ketamine is a useful multimodal preventive adjuvant when combined with general or regional anesthesia, enabling post-ACL repair mobilization under low opioid therapy.

7.1.5. Spine surgery

Lumbar disk surgery under GA associated with either morphine 0.1 mg/kg, ketamine 0.15 mg/kg or morphine + ketamine before surgical incision [93], resulted in less postoperative morphine-PCA in the ketamine + morphine than in the morphine alone patients. The cumulative 24-h morphine consumption was 57% less, and 48% less than in the ketamine only group. VAS scores were lower among the ketamine + morphine patients than in the other patients, especially during mobilization.

7.1.5.1. Pharmacological–clinical relevance. Pre-incisional low-dose ketamine combined with morphine improves postoperative analgesia, and reduces opioid usage and thus side effects, following lumbar disk surgery.

In a group of patients undergoing either cervical or lumbar spine surgery [94] under GA, ketamine 1 mg/kg followed by 42 or 83 μg/kg/h was compared to placebo. Pain scores and postoperative fentanyl-PCA analgesia requirement were lower in the high – than in the low infusion – dose ketamine and the placebo groups after cervical surgery; they were, however, similar after lumbar surgery.

7.1.5.2. Pharmacological–clinical relevance. Intraoperative high bolus dose + low-dose infusion rate of ketamine improves the analgesic effects of fentanyl after cervical surgery, but less so after lumber procedures. No clear explanations exist as for the discordant results in this and in the above-cited report [93], except for its possible different pharmacological interaction with various opioids.

7.1.6. Limb-sparing orthopedic-oncological surgery

Our group demonstrated the usefulness of PCA-morphine 0.7 mg + 5 mg ketamine/bolus/7 min in patients with bone tumors who underwent resection and limb-sparing orthopedic reconstructive interventions [34]. Multimodal drug therapy, including NSAIDs was available on demand. Patients benefited from lower VAS (by 30%) and morphine consumption (reduced by ~35%), and experienced better sedation and satisfaction states (see Section 9).

7.1.6.1. Pharmacological–clinical relevance. Ketamine pharmacological effects are beneficial in orthopedic patients, even in those presenting for surgery already suffering from pain, either due to mechanical or to oncological derivation.

7.2. General surgery

This subtype of operations is ubiquitously present in the literature [31–33,46]. Of special interest are several studies of patients undergoing orthopedic, open abdominal or laparoscopic procedures under GA by our group. When postoperative morphine up to 0.12 mg/kg IV was ineffective in reducing pain to VAS <5/10, ketamine 350 μg/kg was added to a 50% the usual IV morphine bolus dose. This combination was highly successful in satisfactorily reducing pain and analgesics consumption [2,31,32].

7.3. Trauma

An initial bolus dose of 0.5 mg/kg ketamine, either as a single bolus or by incremental doses, aiming to facilitate manipulation, splintage of fractures or extrication in pre-hospital trauma patients, was found to be useful [68]. Ketamine 0.5 mg/kg was prescribed in head injury patients only if demonstrating a normal respiratory rate and a normal pattern of breathing. No neurological sequellae were detected.

7.3.1. Pharmacological–clinical relevance

Ketamine in trauma patients is exceptionally useful, but should be used judiciously, because of the effect on intra-cranial pressure (ICP), especially in spontaneously breathing individuals. This is despite its proven protection on neurons and cerebral tissue [97–108], and since it blocks the toxic effects of excitatory amino acid receptor agonists [109], especially in the presence of cell injury and calcium-propelled ion influx.

7.4. Cardiac interventions and associated sequellae

S-(+)-ketamine-based (1–3 μg/kg + 2–4 mg/kg/h) multi-drug GA protocol (n = 60) was compared to sufentanil (0.25–1.0 μg/kg + 0.5–2 μg/kg/h)-based GA (n = 68) [23]. BIS <60% was propofol- or midazolam-dependent. The minor increase in the pro-inflammatory cytokines IL-6 and IL-8 6 h after aortic unclamping was ketamine-associated, and the anti-inflammatory cytokine IL-10 showed higher levels 1 h after unclamping. Pre- and postoperative plasma levels of TNF-α and tumor necrosis factor-alpha receptor 1 (TNF RI), were similar as were CRP and leukocyte counts. All cardiovascular parameters were comparable in both groups at all time points.

7.4.1. Pharmacological–clinical relevance

The effect of continuous subanesthetic bolus + infusion of S-(+)-ketamine + GA potentiates the pro-inflammatory response to extracorporeal circulation. The link between ketamine and the production of anti-inflammatory system is still unclear.

Serum C-reactive protein concentration was found lower on POD1 in patients treated with ketamine 0.5 mg/kg at induction of anesthesia for CABG [110]. The anti-inflammatory effect of ketamine correlated with improved cognition during the first postoperative week. Conversely, S(+)-ketamine offered no better cognitive performance compared with remifentanil alone [111].

7.4.1.1. Pharmacological–clinical relevance. Ketamine modulates inflammatory responses following GABG. The more recent data, highlighting the role of remifentanil in postoperative hyperalgesia [84], could explain the diversity in ketamine effects between the above reports.

Patients undergoing CABG under GA were given S(+)-ketamine 75 μg/kg bolus + 1.25 μg/kg/min/48 h, or saline, immediately after anesthesia induction [112]. The ketamine group (n = 44) consumed 20% less oxycodone-PCA and the time to its first usage was longer by 25% versus placebo. Ketamine patients were highly satisfied with the analgesic management, but the 48-h VAS rest pain scores, mobilization tests, walking exercises with physiotherapist, and PONV, as well as cognition and delirium rating scales, were all similar between the groups. Major psychomimetic adverse effects were encountered during ketamine infusion.

7.4.1.2. Pharmacological–clinical relevance. Very low (subanesthetic) S(+)-ketamine bolus + infusion as an oxycodone-PCA adjunct exerts an opioid-sparing effect without untoward hemodynamic sequellae after sternotomy in CABG patients. Despite patients' optimal satisfaction, there may appear psychomimetic disturbances. The diverse pharmacological impacts of ketamine in these patients are an example for the multiple neuroeffector effects thus generated. Pain reduction is not linkable to opioids' reduction.

7.5. Thoracotomy

Patients undergoing thoracotomy for minimally invasive direct coronary artery bypass or for lung tumor resection may suffer from postoperative disability. Surgery was undertaken under GA, followed postoperatively by morphine 1.5 mg-PCA or morphine 1.0 mg + 5 mg ketamine/bolus-PCA with a 7-min lockout time. Rescue IM diclofenac 75 mg was also available. One our study lasted for 4 h [47]; another similar one followed the patients for 72 h [33]. In the first investigation [47], the subanesthetic ketamine dose combined with 35% lower morphine dose per bolus provided comparable pain control with the standard morphine bolus dose alone, and fewer adverse side effects. Overall, it allowed for a 45% reduction in morphine consumption. In the second study [33], ketamine enabled a ∼35% reduction in pain scores, 50% in morphine consumption and a shorter PCA length of use compared to the morphine only regimen. Neither hemodynamic, nor respiratory events, nor meaningful psychomimetic events were detected in either study.

7.5.1. Pharmacological–clinical relevance

Ketamine at an extremely low dose, mixed with low-dose morphine-PCA, provides better pain control and less morphine usage for up to 72 h, and allows for quicker disuse of the PCA after trans-thoracic CABG and lung surgery. Either intervention is characterized by painful early recovery.

7.6. Pediatric regional use

The role of ketamine as an adjunct to local anesthetic has gained popularity, including the pediatric population. A review of its use for caudal block [113], included 13 RCTs (n = 584) that fully met specific inclusion criteria (PRISMA) [114]. In these reports, ketamine (0.25–0.5 mg/kg) was added to caudal-based local anesthetics (1.5–2.5 mg/kg) compared with local anesthetic only, in children of different age ranges, undergoing urological, lower abdominal or limb surgery. Ketamine addition prolonged time to first post-surgery analgesia request, and the need for rescue analgesia. The data refute any increase in the rate of adverse events.

7.6.1. Pharmacological–clinical relevance

Caudally administered ketamine, in addition to local anesthetics, prolongs postoperative analgesia with very few adverse effects, compared with local anesthetics alone. The pharmacologically associated neurotoxicity related to the dose of ketamine, the effects of a single versus repeated caudal doses, and the child's age as an independent factor, are still to be determined.

8. Out-of-operating-room procedures

The numbers of out-of-hospital procedures have increased considerably in recent years, and a parallel awareness of the convenience of ketamine use has risen. In one study, 11 patients received either 0.1 mg/kg morphine (8 mg maximum) + saline IV, or 0.05 mg/kg morphine (4 mg maximum) + ketamine 0.25 mg/kg IV before undergoing a wound care procedure (WCP) [61]. Treatment was crossed-over during the next WCP. Pain intensity during the procedures halved with ketamine. Almost all patients reported adverse effects (e.g., strange sensations, hallucinations, blurred vision) with ketamine, and diastolic blood pressure was higher.

An interesting use of ketofol was reported in >1500 patients undergoing various in-office procedures under room air, spontaneous ventilation, non-opioid preemptive analgesia under monitored anesthesia care (MAC) in the presence of BIS. The patients received 1–2 50 mg IV ketamine doses on the top of propofol infusion. No hospital admissions were required, normal oxygenation was maintained in 99% of cases, and a low incidence of ketamine-associated emergence events was reported [115].

Our group has been using ketamine alone or as an adjunct to morphine outside the operating room in all age populations for selective cases of WCP, orthopedic manipulations or magnetic resonance imaging [unpublished data]. Ketamine is routinely employed whenever patients need to be sedated for >15 min and pain is expected to be intense, while maintaining spontaneous respiration and patent airways. The protocol consists of repeated 50 μg/kg top-ups of ketamine every 4–5 min following the first IV bolus of 250 μg/kg. Then, 10–20 mg propofol is added to each bolus. Monitoring of vital signs includes heart rate, non-invasive blood pressure, and pulse oximetry. By local regulations, such patients remain in a monitoring area or the postoperative care unit (PACU)

for 30–60 min, until full coherence is obtained and no side effects are apparent. We recorded no significant unwanted effects of ketamine.

8.1. Pharmacological–clinical relevance

The use of low or subanesthetic doses of ketamine – with or without hypnotics/opioids – is simple, well tolerated at all ages, easily monitored, and is safe in out-of-operating-room settings, including epilepsy-associated procedures [112,116–118].

9. Chronic pain sufferers

Patients presenting to surgery who are already in pain pose a challenge to the anesthesiologist in effectively controlling impending acute pain. Ketamine seems to be a unique optimal drug for such occasions. Perioperative ketamine infusion for ~3 days combined with epidural analgesia produced a meaningful decrease in postoperative chronic pain up to 3 months after oncological thoracotomy [87], and up to 6 months after oncological rectal surgery [88]. These late anti-hyperalgesic effects are difficult to interpret and to reproduce, however, because the incidence and the grade of chronic pain before and after oncologic surgery may be linked to neoplasm recurrence itself, or its original anatomical site, independently of ketamine effectiveness.

Our group has shown sustained and gradual pain control during an assessment period of 48 h in surgical patients already in pain because of pre-existing orthopedic oncology tumor [34]. Ketamine was added to morphine-PCA at a protocol of morphine 0.7 mg + 5 mg ketamine/bolus available every 7 min, compared to 1.5 mg/bolus morphine alone. Such multimodal therapy, which also included NSAIDs, benefited this type of patients with regard to VAS (lower by ~30%), morphine consumption (reduced by ~35%) and better sedation and satisfaction scores.

Two studies [93,94] showing the beneficial effects of ketamine in spine surgery patients with pre-surgery pain were described above (see Section 7.1.5).

In a study of spine fusion procedures [119], patients who had been using morphine for pain before undergoing surgery, were administered 0.5 mg/kg IV ketamine upon induction of N_2O-free balanced anesthesia + 10 μg/kg/min during the procedure until wound closure. All patients were given morphine up to their previous daily morphine-equivalent opiate dose + 0.1 mg/kg morphine before emergence from anesthesia. The ketamine group required 24% less intraoperative fentanyl than placebo; they consumed 30% and 37% less morphine during the first postoperative 24 and 48 h, respectively. They also reported 26.7% reduction in pain intensity in the PACU. 6-week pain reduction of 26% + a 71% reduction in opioid consumption was detected in the ketamine group.

9.1. Pharmacological–clinical relevance

Ketamine is most efficacious in patients with acute on chronic pain, even if using opioids preoperatively. It was calculated that ketamine efficaciously reduces early and late postoperative pain when administered on top of preoperative daily 0.56 mg/h morphine IV or 40 mg morphine-equivalents orally.

10. Acute pain sufferers

Prolonged acute pain, especially that of oncologic or trauma origin, that involves neuron-physiological changes, is often difficult to control and is seldom completely controlled by opioids. Our group treated eight patients with severe acute pain, three of whom suffered from new-onset oncologic metastatic bone pain, and five had exacerbation of previous vascular and orthopedic pain [120]. Pain was associated with hyperalgesia and allodynia in two patients and with phantom pain in a third one. Tolerance to opioids had developed, and high IV doses of morphine and equivalents (meperidine, fentanyl, oxycodone, etc.) or epidural analgesia were ineffective. Several patients became opioid-dependent and could not be weaned from assisted ventilation. Pain was controlled with the addition of up to 2 g ketamine to 0.5–1.0 g morphine/24 h infusion. Two–three days later, the pharmacological doses of morphine were tapered, followed by tapering ketamine, and then stopping both within 5–10 days, replacing them with oral regimens compatible with outpatient care (i.e., oxycontin). There was no rebound effect, ketamine-associated sequellae, or persistence of opioid dependence.

10.1. Pharmacological–clinical relevance

Ketamine is an efficient pharmacological adjuvant for intractable severe acute pain, caused by metastasis, trauma, chronic ischemia, or recent central neuropathic pain, most of which following surgery. It is effective even when large pharmacological doses of IV, epidural or oral opioids prove ineffective and when signs of tolerance have developed.

11. Dose protocols – summary

Ketamine induces a brief period of analgesia associated with minimal and leveled hypnosis, if given alone, but it is most beneficial, even long-term, when used as part of a multimodal plan perioperatively [121]. Non-IV use of ketamine is not within the scope of this review (for an overall therapeutic description, see [122]).

11.1. Perioperative administration

Currently, ketamine is administered in "subanesthetic doses" as follows:

a. Bolus dose: 250–500 μg/kg, adjuvant to morphine/fentanyl/remifentanil-based GA.
b. Infusion dose: 0.2–0.3 mg/kg/h.
c. In combination with epidural anesthesia, reduce ketamine bolus to ~50 μg/kg and the IV infusion dose.
d. To prevent postoperative hyperalgesia (especially at the end of remifentanil- or isoflurane-based anesthesia [85,121,123]): before stopping the opioid, administer morphine bolus 50–100 μg/kg + ketamine 250–350 μg/kg to prevent the patient from awakening into severe pain. Some patients may require a series of such boluses (3–4, one every 5–7 min) to optimally preempt hyperalgesia [31,120].
e. The ED50 and ED95 of ketamine for the prevention of postoperative hyperalgesia (as after remifentanil-based anesthesia) in patients undergoing laparoscopic cholecystectomy were found to be 0.24 and 0.33 mg/kg, respectively [124].
f. Ketamine blood concentrations ~100 ng/ml are considered efficacious to counteract hyperalgesia while producing minimal side effects [125].

11.2. Postoperative administration

Ketamine can be administered either by repeated boluses, when combined with continuous infusion – with or without opiates, or by PCA.

a. If pain is still ≥5/10 by NRS after the administration of an appropriate IV dose of opioid (e.g., 0.1 mg/kg morphine), possibly

coadjuvated with various rescue drugs, add 50% the opioid bolus (e.g., 1 mg if the standard IV bolus is 2 mg) + 25 mg (~350 μg/kg) ketamine IV. Our group has demonstrated that some patients require up to four such boluses (1 every ~10 min) to optimally and constantly suppress early hyperalgesia [31,32], and reduce pain to an acceptable level (≤5/10 NRS).

b. IV-PCA of ketamine + opioid is started at the patient's self-rated pain score ≥5/10 NRS (or ≥50/100 mm VAS). Optimal lockout time is 5–7 min.
c. Our IV-PCA devices are programmed to deliver 0.7 ml of the above-cited ketamine + morphine combination compared to 1 ml when morphine is the only delivered drug [2,32–34,47].
d. Most patients benefit from pre-boosting the PCA with boluses of 3–5 mg morphine + ketamine 250 μg/kg each.
e. PCA-morphine-to-ketamine mixture ratio is usually 1:1 or 1:2. Our protocols consist of adding 100 mg morphine + 250 or 500 mg ketamine, making a total solution of 50 ml of 0.9% saline.
f. An infusion regimen should aim at a plasma ketamine concentration of 0.06–3 mg/l [126].
g. A review by Grass describes modes of PCA administration of ketamine (and non-ketamine) for postoperative analgesia, guidelines, potential adverse effects and recommendations for monitoring and treatment precautions [127].

12. Final words

In spite of the fact that there are no evidence-based data to link the length of infusion time to the pharmacological anti-hyperalgesic duration of action, it seems reasonable to consider that the longer ketamine is administered perioperatively, the more effective and the longer will the effect last. Thus, while a pre-incision dose of 0.15 mg/kg ketamine followed by 1.5–2 μg/kg/min (~6–8 mg/h) proved effective in reducing short-term postoperative pain and opioid consumption [86], a 0.5 mg/kg IV bolus + 0.25 mg/kg/h (4 μg/kg/min) infusion during GA was effective in providing long-term analgesia [88].

Up-dated guidelines indicate that unlike before, ketamine administrations for minor oropharyngeal procedures and head trauma are not considered anymore as contraindication. Co-administration of prophylactic anticholinergics is no longer recommended, and benzodiazepines may benefit adults but not children [128].

13. Part II: gabapentinoids

13.1. Introduction

Uncontrolled pain can result in sympathetic stimulation, tachycardia, or myocardial ischemia in susceptible individuals, all of which may impair early and late rehabilitation. The acute postoperative pain itself can also transform into chronic pain that can have major negative effects on the individual's quality of life. Multimodal analgesia (see Part I) represents a comprehensive approach to postoperative pain management [129], combining analgesics with differing mechanisms of action, aiming at targeting various pathways and neurotransmitters involved in nociception and hyperalgesia. Thus, the use of non-opioid adjuncts can act more specifically and therefore at lower doses, as well as reduce opioid requirements and their side effects (e.g., nausea, vomiting, sedation, respiratory depression, urinary retention, constipation, pruritus). Also, minimization of intraoperative opioid use would reduce the development of perioperative opioid tolerance [130–132].

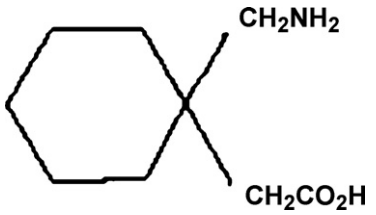

Fig. 2. Gabapentin (GBP) chemical presentation.

Gabapentinoids are anticonvulsant drugs. There is ongoing search for evidence-based data on their role in acute pain treatment, but the heterogeneity of the relevant studies with respect to quality, design, cohorts and types of surgery, and outcome measures complicate such efforts. The 'negative' trials are not always accepted for publication [133]. An overview of the subject can be found elsewhere [134–136].

14. Pharmacology

During the past few years, two major drugs of the gabapentinoid group have been increasingly used as part of multimodal analgesia regimens in the perioperative setting. Overall, they helped to spare opioid use and reduce postoperative pain [137,138]. Despite their name, gabapentinoids do not bind to the gamma aminobutyric acid (GABA) receptors, $GABA_A$ or $GABA_B$.

Gabapentin (GBP, Neurontin) [1-(aminomethyl)cyclo-hexane-acetic acid] (Fig. 2), an alkylated analogue of gamma aminobutyric acid (GABA), was introduced in 1993 in Europe and 1 year later in the USA. It was first developed as an anticonvulsant drug; its potentials for the treatment of neuropathic pain were suggested in the mid 1990s [139–141], and confirmed by large placebo-controlled, double blind trials [142,143].

Pregabalin (PGL, Lyrica) [(S)-(+)-3-(aminomethyl)-5-methylhexanoic acid] (Fig. 3) was introduced in Europe and the USA a decade after GBP, and then became commercially available. It has a similar pharmacological alkylated GABA analogue structure. It is currently licensed for adjunctive treatment of partial seizures with or without secondary generalization, and for use in peripheral and central neuropathic pain and generalized anxiety disorders [144,145]. Pregabalin is considered an alternative drug for treating or preventing opioid dependence, and possibly prevent hyperalgesia [146]. It has been used off-license for a variety of other conditions, including panic disorder and fibromyalgia. Its mechanism of action is probably the same as GBP, but it has a superior pharmacokinetic profile [147] (see below).

Animal studies have shown that GBP does not inhibit sustained repetitive firing of sodium action potentials. It appears to interact with cortical neurons at auxiliary subunits of voltage-sensitive calcium channels, but the relationship of this action to functional activity is unclear. GBP crosses brain cell lipid membranes via L-system amino acid transporters. Both PGL and GBP bind to the α2δ subunit of the neural voltage-dependent calcium channel, which decreases the release of neuro-peptides, including glutamate, nor-epinephrine, and substance P [148,149]. These calcium channels regulate the movement of calcium (as calcium ions, or

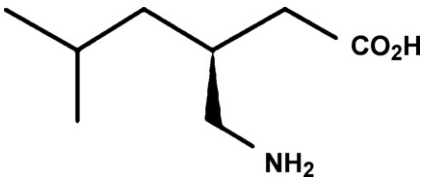

Fig. 3. Pregabalin (PGL) chemical presentation.

Ca^{2+}) into cells, and calcium influx is needed to trigger the release of several neurotransmitters from pre-synaptic neurons (see Fig. 1). Such up-regulation of the α2δ subunit plays an important role in the sensitization process in acute pain [150]. By decreasing the hyper-excitability of dorsal horn neurons that had been induced by tissue damage, gabapentinoids also modulate postoperative pain [151,152], hyperalgesia and central sensitization [153]. GBP has been suggested to antagonize the NMDAR and block its calcium channels [154], and it seems to inhibit ectopic discharge activity from injured peripheral nerves [155]. One study on PGL in healthy volunteers exposed to electrically evoked pain and hyperalgesia, demonstrated that it decreased the areas of mechanical hyperalgesia and dynamic touch allodynia [156].

15. Metabolism

Both gabapentinoids are available as oral preparations only. GBP is absorbed in the small intestine by a combination of diffusion and "facilitated transport" via a receptor that provides a saturable L-amino acid transport mechanism [157]. As such, GBP bioavailability varies inversely with its dose: the lower the dose, the higher its bioavailability [158]. GBP is not metabolized in humans but rather is eliminated unchanged in the urine [159]. Since it undergoes first-order kinetic elimination, renal impairment decreases GBP elimination in a linear fashion with creatinine clearance [159]. The elimination half-life of GBP is 4.8–8.7 h [158,160,161], and is removed by hemodialysis, so that patients should receive a maintenance dose after each treatment [162]. Unlike other anticonvulsant drugs, it does not induce or inhibit hepatic microsomal enzymes (drug–drug interaction). Antacids reduce the bioavailability by ~20% when given concomitantly or up to 2 h following GBP administration [163]. The therapeutic level of GBP is 2–15 μg/l.

PGL demonstrates highly predictable and linear pharmacokinetics, a profile that makes it easier to use in clinical practice than GBP. Its absorption is extensive, rapid, and dose independent. Peak plasma concentration is reached within <1 h, and steady state is achieved within 24–48 h [147]. PGL's mean elimination half-life ($t_{1/2}$) is 6.3 h, and it possesses dose-proportional maximal plasma concentrations. PGL does not bind to plasma proteins and is excreted virtually unchanged (<2% metabolism) by the kidneys [147,164]. Dose adjustment may be necessary in patients with renal insufficiency. It does not undergo hepatic metabolism nor does it induce or inhibit liver enzymes, such as the cytochrome P_{450} system. Therefore, PGL is unlikely to cause, or be subject to, pharmacokinetic drug–drug interactions. The pharmacokinetic profile of PGL and its central nervous system bioavailability were studied by using cerebrospinal fluid (CSF) as a convenient sampling port in humans [165]. When a single oral dose of 300 mg was administered, the peak CSF of PGL concentration was reached within 2 h, which is consistent with a 1 h time to peak plasma concentration after a 50 mg dose [164]. A dose of 300 mg has the greatest likelihood of achieving a maximum pharmacological effect at the spinal level at 8 h or more after oral dosing. Some researchers recommended administering the drug up to 4 h before surgery, if anti-allodynic effect is to be attained at the start of the postoperative period, and assuming surgery lasts 2 h [165].

16. Untoward effects

A. Gabapentinoids are well tolerated and have few serious adverse effects. The most common transient side effects include somnolence and dizziness [134]. Headaches, balance problems, peripheral edema, sweating and dry mouth, and gastrointestinal symptoms, have also been described. Their severity is generally time- and dose-related, and can be mitigated with dose adjustment even after short-term administration. Blurred vision after 150 mg/d of PGL disappeared <12 h of its detection [166].
B. Ramsay [167] reported that somnolence (20%), dizziness (18%), ataxia (13%) and fatigue (11%) were the most common side effects after long-term treatment.
C. Nausea, vomiting, or both, as well as sedation, dizziness, headache, blurred vision, pruritus, and lack of concentration, have been reported in association with acute pain treatment [168,169].
D. The most common side effect after a single 300 mg dose of PGL administered 1 h preoperatively in patients undergoing total abdominal hysterectomy, was nausea/vomiting and dizziness [170].
E. Sedation (29.2%), dizziness (22.2%), dizziness/somnolence (4.21%) and headache [135], all of which are dose dependent, were among the most frequent adverse effects of PGL during chronic treatment. Other reported adverse effects included drowsiness, dizziness, fatigue, nystagmus, headache, blurred vision, and postoperative nausea and vomiting [166,171].

Noteworthy, interpretation of the data on analgesia and adverse effects must take into account that the number of studies, and thus the sample size, are still relatively small.

17. Clinical notes

A. There are no evidence-based data to establish the optimal duration of postoperative gabapentinoid treatment.
B. There are no evidence-based data to establish whether preoperative administration of either drug is better than postoperative delivery.
C. There is no proven effect of GBP on time of post-anesthesia care unit (PACU) discharge or return to work [172].
D. Several RCTs failed to find differences in the time that elapses between the end of the surgery and the first analgesic request for either drug [171,173].
E. Pain reduction is not always associated with reduced opioid consumption.
F. Each drug is given in a multimodal modality and not used as a sole agent for the management of acute postoperative pain.
G. Results after gynecological procedures, for example, do not correlate with those after abdominal or orthopedic surgery. This is due to different types of pain and dose variability. Extrapolation of the methodology of use and dose ranges between various types of surgery awaits more sound data, and this still mandates cautious and judicious use.
H. Optimal pharmacological efficacy of PGL is achieved with doses ≥150 mg preoperatively followed by b.i.d. for the ensuing 24–48 h [166,171].
I. One study in children found that long-term GBP was safe at doses of 26–78 mg/kg/day in 52 children and adolescents (mean age 11.1 years) [174]. The following notes apply for both GBP and PGL [175,176].
J. GBP exerts perioperative anxiolytic properties [177–179].
K. GBP prevents and/or reverses/attenuates postoperative opioid tolerance [180].
L. Similarly to ketamine, GBP is effective in the treatment of postoperative pain [151,176,181–183] and in the inhibition of central sensitization [184,185], i.e., hyperalgesia. It also prevents mechanical hyperalgesia [186,187].
M. GBP is an effective and safe adjuvant to morphine [174,188,189], including cases of pain tolerance (as shown by cold stimulation in volunteers) [190] and for the reduction of neuropathic cancer pain [191].

N. Gabapentinoids have been tested in a number of different surgical procedures, although in small cohorts, and were found useful adjuvants to analgesics, allowing for their dose reduction. For example:

a. knee surgery, when associated with neuroaxial regional anesthesia [192]
b. abdominal and pelvic surgery [193–200]
c. musculoskeletal surgery [201–208]. Note that three out of six trials failed to demonstrate a decrease in pain scores or an opioid-sparing effect in the early post-surgical period [202,203,206]
d. head and neck surgery [209–211]
e. breast surgery [210–215]
f. varicocele surgery [216]
g. thoracic surgery [217].

18. Drug combinations

A. GBP appears to reduce intra- [216] and post-surgery [210,216] analgesic consumption or the number of patients requesting analgesics [218] when added to dexamethasone [216], rofecoxib [200,210] or lornoxicam [218].
B. GBP–acetaminophen combination provided better pain control, and reduced PCA-morphine consumption compared with GBP alone or placebo after abdominal hysterectomy [219].
C. Perioperative GBP [220] or its combination with dexamethasone [216] or rofecoxib [200] reportedly had a significant synergistic reduction of PONV versus placebo.
D. Gabapentinoids and ketamine.

The perioperative pharmacological interventions, as mentioned in Part I, advocate the application of different drugs due to their specific mechanisms of action within the multimodal analgesia regimen. These opioids and non-opioid systemic drugs, or regional anesthetics, currently form postoperative pain protocols and should be examined via various aspects, including their reciprocal effects or the early versus late post-surgery pain control, alone or together. The role of NMDAR antagonist, ketamine, in reducing post-injury central sensitization, morphine consumption and the evolvement of opioid tolerance, when administered for post-surgical pain, was extensively depicted in Part I: ketamine. Such early benefits in the postoperative period are well established, but the long-term effects remain less encouraging [88].

The gabapentinoids apparently prevent the release of central nociceptive neurotransmitters [221]. Clinically, they provide effective postoperative analgesia by inducing neuroplastic changes in the early postoperative period, although originally this drug has been assigned for chronic pain.

Since late central sensitization is an important part in the evolvement of acute into chronic pain, integrating mechanism of peripheral nociceptive impulses and central neuroplasticity, the effects of adjuvants while detecting pain thresholds following repetitive electrical cutaneous and suprathreshold responses, were analyzed in healthy volunteers [222]. Authors evaluated temporal summation of the wind-up process of wide dynamic range neurons of repeated nociceptive electrical stimuli. Patients received three PGL 300 mg oral doses each 12 h, while ketamine IV bolus 0.5 mg/kg was administered 3 h and 40 min after the PGL dose (to prevent potential of a carryover effect from PGL), followed by 9 mg/kg/min/20 min ketamine on the first day of the noxious stimuli, or placebo. This protocol was repeated after 10–14 days, replacing ketamine with placebo. The results documented temporal summation threshold increase with ketamine, compared with placebo; suprathreshold pain responses were thereby reduced. PGL affected neither of the parameters.

18.1. Pharmacological–clinical relevance

In the given anti-nociceptive approach, PGL does not affect early temporal summation and wind-up process, while ketamine does.

Despite the clinical and pharmacological basis for the combination of both types of adjuvants, there are very few clinical studies where ketamine and GBP were used jointly or comparably. Sen et al. [223] studied 60 patients undergoing elective abdominal hysterectomy with salpingo-oophorectomy under fentanyl + sevoflurane-based GA. Patients received either oral placebo capsule 1 h preoperatively + bolus + infusion of saline (control), oral placebo capsule + 0.3 mg/kg IV bolus + 0.05 mg/kg/h infusion of ketamine until the end of surgery, of oral GBP 1.2 g + bolus + infusion of saline. Postoperative MO-PCA analgesia and oral analgesics were provided postoperatively. The VAS pain scores, both when lying or sitting, were lower in the GBP compared with the controls and the ketamine group. PCA usage dropped in the ketamine and GBP groups soon after surgery compared to controls. Satisfaction rates improved in the two drugs' groups. The return of bowel sounds, passage of flatus, ambulation, nausea and vomiting, and hospitalization times, were similar among the three groups.

The incisional site pain scores at the 1-, 3-, and 6-mo were lower in the GBP compared with the ketamine and control groups. GBP group's daily activities were less painful compared with the ketamine and control groups at 1- and 3-mo follow-up, but comparable at 6-mo follow-up.

18.2. Pharmacological–clinical relevance

Preoperative administration of GBP, and pre- and intraoperative low-dose ketamine, as parts of a multimodal analgesic regimen that includes MO-PCA and oral analgesics, improve early pain control, and decreases morphine consumption. GBP partially reduces the late (chronic) pain development, but ketamine does not. Besides the different pharmacokinetics and dynamics of the drugs, the different effects may be attributed to the ketamine low dose and the short duration of its administration.

As mentioned throughout the review, multimodal analgesia benefits from the different though specific mechanisms of action of various analgesics, thus better attenuating postoperative pain and further reducing side effects. It has also been suggested that the use of more than two multimodal drugs would have an extra value of effectiveness [224]. Following this assertion, patients undergoing hip arthroplasty under combined spinal (plain bupivacaine 3 ml) and monitored anesthesia care (propofol infusion 10 mg/ml) were investigated [225] for the effects of preoperative GBP 1.2g + dexamethasone 8mg + ketamine 0.15 mg/kg + paracetamol 1 g + ketorolac 15 mg at the end of surgery ($n = 24$), versus placebo + paracetamol + ketorolac ($n = 18$). Postoperative analgesics consisted of MO-PCA 2.5 mg/10 min + paracetamol 1 g t.i.d. + ketorolac 15 mg t.i.d. The total 24-h pain scores, mobilization and 4-h rest pain scores were lower in the drug combination than in the placebo group; morphine consumption was only slightly lower, and side effects (PONV, dizziness, sedation, hallucination) were similar among the groups.

18.3. Pharmacological–clinical relevance

Preoperative GBP + dexamethasone + low-dose ketamine bolus (>2 multimodal drugs) reduce the overall 24-h and mobilization pain scores, particularly the moderate-to-high ones; analgesic consumption did not change. As frequently occurring when studying antinociceptive drugs, changes in pain VAS do not necessarily parallel morphine consumption, possibly due to yet lack of understanding of the pharmacological interaction among drugs, drug relatively low dose, short-term peak blood levels, or a type 2 error,

as herein suspected. Since no prolonged effect was herein evidenced, a preemptive/preventive effect is left for further studies.

In an interesting study [226], patients with neuropathic pain secondary to spinal cord injury, received both 80 mg/500 ml NS ketamine infusion/5 h daily/1 week + 300 mg GBP t.i.d. ($n = 20$), or placebo (infusion + 300 mg GBP t.i.d./1 week, $n = 20$). Both treatments reduced pain scores compared with pretreatment status; ketamine enabled additional pain score improvements, however only during infusion and for 2 weeks after its termination. Either treatment controlled pain at 3 and 4 weeks similarly after infusion termination, and were tolerated well, requiring no treatment for side effects (delusion [ketamine], dizziness [GBP]).

18.4. Pharmacological–clinical relevance

Multi-day low-dose ketamine infusion as an adjuvant to GBP for post-spinal cord injury chronic pain is safe and efficacious in reducing pain. However, it lasts only 2 weeks after infusion termination.

19. Clinical illustrations of use

19.1. Adjuvants to GA

Various doses of preemptive GBP (300–1200 mg) were shown to decrease the severity of postoperative pain and total opioids (e.g., fentanyl) consumption during the first 24 h, as after myomectomy [171,227]. The optimal preoperative dose of GBP, 600 mg, has been established in a dose–response study by Pandey et al. [204] in patients undergoing lumbar discectomy. At higher doses, patients exhibited numerous and more intense side effects with no additional reduction in pain or lower dose of postoperative fentanyl. The median effective dose of pre-emptive GBP on postoperative morphine consumption after posterior lumbar spinal fusion was found to be 21.7 mg/kg [228]. 4 mg/kg of GBP was administered preemptively in patients undergoing single-level lumbar discectomy under GA [205] decreased the severity of postoperative pain by ~50% and reduced the requested amounts of fentanyl by 45%.

19.1.1. Orthopedic cases

While several pre- and postoperative GBP trials have demonstrated an early postoperative reduction in movement-evoked pain [169,195,198,200,201,209,212], continuing GBP into the early rehabilitation period led to decrease pain and improved functional recovery (i.e., a greater range of motion) for several days postoperatively.

Patients undergoing abdominal hysterectomy under GA received 400 mg GBP starting 18 h preoperatively and followed by 400 mg 6 h during the following five PODs. The 48-h PCA-morphine consumption was 20% lower than in the controls, and paracetamol/codeine was used 50% less. Pains VAS at rest and after coughing were similar. One month post-surgery, 81% controls reported pain in the surgical area compared to 36% GBP recipients, and 41% versus 28% consumed analgesics, respectively [194].

A single preoperative dose of GBP 1200 mg followed by GA + morphine 0.1 mg/kg and postoperative morphine-PCA in patients undergoing knee surgery [201] demonstrated a 50% reduction in VAS anxiety scores in the GBP group compared to the controls. VAS pain scores did not change; the time to first request of analgesia was 15 times longer for the GBP patients. The 48-h cumulative morphine consumption of the GBP patients was 50% less. The maximal passive and active knee flexions at 24 and 48 h after surgery improved with GBP.

Unlike these latter patients, those who received GBP 600 mg preoperatively and GBP 600–1400 mg postoperatively t.i.d./4 days, used less PCA-morphine for 48 h and performed better active assisted knee flexion on POD 2,3 [192].

Various RCTs and reviews suggest that PGL is also efficacious for short-term acute post-surgical pain treatment [168,229–231]. Long-term effects await further confirmation.

19.1.1.1. Pharmacological–clinical relevance.

Gabapentinoids combined with GA and opioids for orthopedic or general surgery, are efficacious both at early and late (48 h–1 month) periods in reducing pain, performing better post-orthopedic movements and sparing opioid consumption. Perioperative anxiety is also minimized. Side effects intensify as the dose of GBP increases.

Elective lumbar discectomy due to chronic lumbar sacral radiculopathy under fentanyl- and sevoflurane-based GA + subcutaneous bupivacaine infiltration was undertaken with or without PGL 300 mg 90 min preoperatively + 150 mg at 12 and 24 h postoperatively [232]. VAS anxiety score pre-incisionally was 4-fold lower in the PGL group compared to the evening before surgery. Pain scores at 3 months were lower and satisfaction questionnaires revealed better results. Patients were all back at work at 3 months compared to 75% of the placebo recipients.

19.1.1.2. Pharmacological–clinical relevance.

PGL 300 mg preemptively and 150 mg/12 h thereafter (1) leads to better pain containment, function, and quality of life at 3 months after lumbar discectomy, (2) increases pain perception threshold in the lower limbs 24 h postoperatively, (3) reduces the preoperative anxiety score, and (4) quickens rehabilitation 3 months after surgery.

19.1.2. General surgery cases

Hill et al. [168] and Jokela et al. [171] also found that perioperative PGL administration had a beneficial effect on postoperative pain scores and analgesic requirements 24 h after dental and gynecological surgery.

Preoperative PGL (150 compared to 300 mg) or diazepam 10 mg, before and after surgery, was tested in 90 patients undergoing laparoscopic hysterectomy under remifentanil-based GA + dexacort and droperidol, followed by postoperative PCA-oxycodone. Each PGL dose differentially (300 >150 mg) decreased the 48-h oxycodone consumption, but pain level remained similar. The 300-mg regimen was associated with a higher rate of adverse events (dizziness, blurred vision, and headache) for 3 days than the 150-mg regimen [173]. Pain, analgesic consumption, the times to the first rescue analgesic dose, and the usage of rescue drugs were equal in the three study groups. Pain VAS scores at rest, in motion and when coughing, and satisfaction rates, were similar. The incidence of PONV, drowsiness, dry mouth, swelling of limbs and lack of concentration did not differ among the groups. The incidence of blurred vision was detected in both PGL groups for a short period; pruritus was the lowest in the 300 mg group.

19.1.2.1. Pharmacological–clinical relevance.

PGL pre-empting hysterectomy under remifentanil-based GA + dexacort and droperidol is useful either in 150 or 300 mg dose, and spares the use of postoperative PCA oxycodone. Nevertheless, the higher the gabapentinoid dose is, the more intense are the side effects.

A single dose of PGL 300 mg given at 1 h pre-sevoflurane GA + morphine 0.1–0.2 mg/kg intraoperatively and postoperative PCA-morphine, was analgesically beneficial, but associated with substantial – though similar to controls – rates of PONV and dizziness after abdominal hysterectomy with/without salpingo-oophorectomy compared to lorazepam 0.5 mg [170]. Pain VAS scores and the 24-h total morphine consumption in the PGL patients were lower than the controls'. Satisfaction scores were 2-fold better in the PGL patients.

Paech et al. [233] reported that PGL 100 mg given 1-h preoperatively had no effect on pain and postoperative fentanyl requirements after day-care minor gynecological interventionn.

This is despite patients experiencing post-discharge side effects, such as mild headache or drowsiness.

19.1.2.2. Pharmacological–clinical relevance. PGL seems to demonstrate pharmacological efficacy at doses ≥150 mg, starting pre-incisionally, and re-administered b.i.d. for 1 day or more. Adjuvated with remifentanil- or sevoflurane-based GA, it rises pain threshold and reduces postoperative demand for rescue analgesics. Satisfaction rates are also higher than in the controls. As the drug dose increases, the intensity and rate of the side effects rise as well. Noteworthy, reports on untoward effects appear inconsistent, possibly because of the different types of interventions, cohort heterogeneity, intraoperative opioid protocols, drug combinations, etc.

19.2. Adjuvants to epidural/regional block

The use of GBP with regional anesthesia (spinal, epidural or peripheral nerve blocks) potentiates the efficacy and the duration of action of the neuronal blockade for several postoperative hours [137,234]. Furthermore, the opioid-sparing effect of GBP becomes evident once the peripheral nerve block dissipated [234]. Turan et al. [235] demonstrated that premedication with oral GBP (1.2 g) decreased tourniquet-related pain and improved the quality of anesthesia during hand surgery under intravenous regional anesthesia.

A single preoperative GBP 800 mg dose given 2 h before surgery neither improved postoperative analgesia nor spared the use of multi-drug analgesics in patients given 0.3 ml/kg of 0.5% ropivacaine for interscalene brachial plexus block + sevoflurane-remifentanil-based GA for arthroscopic shoulder surgery [202].

19.2.1. Pharmacological–clinical relevance

GBP is useful in combination with regional and neuroaxial anesthesia, although the use of drugs implicated in potentiating hyperalgesia may counteract the anti-hyperalgesic effects of GBP.

Patient-controlled epidural analgesia (PCEA) for late termination of pregnancy (LTOP) [166] was combined with PGL 150 mg/12 h. GBP was shown to intensify epidural analgesic effects compared to prazepam 10 mg/12 h, to reduce requests for ropivacaine 0.2% by-patient bolii, and fewer (25%) by-physician administrations of rescue doses. There was no excessive sedation, vertigo, or dizziness, possibly because of the PCEA rather than opioid usage observed in other studies [169,170,173,233]. Importantly, unlike the findings in other settings, such as on orthopedic procedures [208] that evoke somatic pain, LTOP and labor pain transmit largely visceral pain.

19.2.1.1. Pharmacological–clinical relevance. PGL coadjuvates other drugs to (1) reduce visceral pain, (2) limit pain sensitization process, (3) potentiate epidural analgesics, and (4) modulate the affective component of pain, probably related to the decreased level of anxiety. The latter (4) can be linked to the neuro-psychotropic effects of PGL on pain, i.e., physical suffering and anxiety, thereby reducing them.

19.3. Pregabalin in the elderly

A distinctive study where 75 patients >75 years of age were treated with 150 mg of PGL 1 h before CABG under fentanyl-sevoflurane-based GA, and 75 mg b.i.d. for five PODs, or placebo, was recently reported [236]. Postoperative opioid consumption was spared by ∼45%, the incidence of confusion on the 1st POD was lower, but sedation increased, and the time to extubation

Table 1
Clinically important characteristics of gabapentinoids for acute pain, resulting from randomized controlled trials (RCTs).

Parameters	Gabapentin	Pregabalin
Qualified controlled substance	None	Substance V
Absorption	Dose dependent[a]	Dose independent
Time to maximal absorption, hours	2–3	0.5–1.0
Bioavailability (%)	30–60	>90
Plasma protein binding (%)	<3	0
Metabolism	None	None
Drug–drug interactions[b]	Unlikely	None
Form of excreted compound	100% unchanged	97% unchanged
Elimination half-life ($t_{1/2}$), hours (range)	4.8–8.7	5.5–6.3
Potency (equivalent)	1	5
Mode of administration	Oral, t.i.d.	Oral, b.i.d.
Preoperative protocol, hours (range)	1.5–3	12, 1.5
Preoperative doses, mg (range)[c]	300–1600	100–300
Acute pain daily dose, mg (range)	1800–4200[d]	600–1200[e]
Dose adjustment with renal function	$\sim C_{CL}$	$\sim C_{CL}$
Mostly adjuvant to	GA	GA
Types of surgical intervention	Various	Various
Investigated duration of treatment, days[c]	7	7
Proven maximal duration of effect, months[c]	6	3
Postoperative co-administration	PCA, various drugs	PCA, various drugs
Opioids sparing effect (%)[c]	32–50	16–60 (40[f])
Overall analgesics' sparing doses	MO, fentanyl, oxycod, NSAIDs	MO, fentanyl, oxycod, NSAIDs
Proven late analgesic and anti pain sensitization effects	Yes	Yes
Main side effects[g]	Dizziness, sedation[h]	Dizziness, sedation[h]

t.i.c. = trice daily; b.i.d. = twice daily; C_{CL} = creatinine clearance; GA = general anesthesia; PCA = patient-controlled analgesia; MO = morphine; NSAIDs = non-steroidal anti-inflammatory drugs.

[a] The higher is the dose, the lower is the absorption rate.
[b] Except for antiacids that reduce gabapentinoids' efficacy by ∼20% if administered together or within 2 h from each other.
[c] Confirmed in RCTs.
[d] Ref. [237].
[e] Ref. [181].
[f] Epidural anesthesia/analgesia.
[g] Dose dependent.
[h] Sedation may be potentiated if ethanol or benzodiazepines are added.

was longer. PGL patients experienced less pain immediately after surgery, and 3-mo movement pain. No differences were found with regard to PONV.

19.3.1. Pharmacological–clinical relevance

Despite the small cohort, this study highlights the usefulness and safety of PGL at reduced doses in elderly cardiac individuals for reducing early and late pain, opioid consumption and early postoperative confusion. Sedation is prolonged without unwarranted effects.

20. Summary and clinical remarks (Table 1)

20.1. Effects on acute and chronic pain

When given as adjuvants to GA or epidural anesthesia, GBP and PGL are effective in reducing both pain intensity and opioid consumption after surgery ( ). The analgesic potential of gabapentinoids per se in comparison with other standard postoperative analgesic regimens is still not clear. There are no conclusive data regarding the optimal gabapentinoids doses and duration of postoperative treatment that would best prevent late hyperalgesia. This is mainly because only a few RCTs have followed the patients long enough. As such, their efficacy in preventing the establishment of chronic postoperative pain still needs to be elucidated in future studies.

20.2. Effects on PONV

GBP and PGL seem not to have much influence on the prevention/occurrence of PONV [170,231,236].

20.3. Effects on anxiety

The GBP doses (600–1200 mg) and GBP 150–300 mg preemptively, are effective in reducing anxiety both in conjunction with orthopedic or general surgery [147,166,168,171,177–179, 192,201,232], as well as in non-interventional occasions [178,179]. Nevertheless, White et al. [237] reported that a single dose of PGL of 75–300 mg 90-min preoperatively in 108 patients increased perioperative sedation in a dose-related fashion; neither dose reduced the state of anxiety (and pain scores) in patients undergoing minor procedures under fentanyl-desflurane-remifentanil-based GA + intraoperative ondansetron + dexamethasone, and postoperative fentanyl 25–50 μg IV boluses per request. The most likely explanation for the inconsistent anxiety results between this and previous reports (see top of paragraph) could relate to the short time interval from administration of PGL to induction of anesthesia (namely, 60–90 min), the low PGL dose, and relatively low baseline levels of anxiety in patients undergoing minor surgery compared to those subjected to major operations. Noteworthy, sedation and anxiety questionnaire were used dissimilarly among the cited studies.

20.4. Current practice and a note of caution

GBP has been used at a dose ~1200 mg before anesthesia and surgery [238]. The postoperative doses range between 400 and 600 mg t.i.d. for 3–4 days. PGL can be started preemptively at a dose of 150 mg, at which it will be effective in reducing postoperative pain, in addition to having opioid-sparing effects [147]. A 300 mg dose of PGL administered after surgery was more effective than 400 mg ibuprofen in attenuating acute dental post-procedural pain [168]. These regimens also provide reduced anxiety and minimize the need for rescue analgesia. Late (3-mo postoperative period) psychological and physical benefits were identified following various interventions, such as orthopedics [166,194,239]. No large amount of data exists to establish the effectiveness of relevant doses of gabapentinoids in pre-empting or preventing postoperative pain (i.e., pre- versus post-surgery administration).

The most valued information regarding the effects of gabapentinoids, such as morphine consumption, derives from different types of surgery in which PGL and GBP had been used. However, not all operations have the same opioid requirement perioperatively. Even where intraoperative opioid requirements are comparable, different subgroups could lead to dissimilar results. Also, opioid consumption would probably change where PGL, for example, had been administered both 1 h before and 12 h after operation, compared to studies in which it was only administered 1 h before the intervention. These cohorts would have varying postoperative requirement for opioids as well. Furthermore, some protocols included intraoperative opioids, acetaminophen, non-steroidal or various other drugs that have been given either before operation or by infusion after operation, all resulting in hardly comparable protocols. Finally, the use of ondansetron, droperidol, dexamethasone, and other drugs, is known to reduce postoperative nausea and vomiting, rather than PGL alone. Thus, it is hard to extrapolate from the results in one study to another, and until a convincing large-scale of data has been gathered regarding these drugs, cautious use of these adjuvants still warranted.

Acknowledgements

The author wishes to thank Dr. PM Ekstein for her valuable suggestions, and Esther Eshkol, for proof-editing the text.

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