

REVIEW ARTICLE



Gabapentin: a multimodal perioperative drug?

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Gabapentin is a second generation anticonvulsant that is effective in the treatment of chronic neuropathic pain. It was not, until recently, thought to be useful in acute perioperative conditions. However, a growing body of evidence suggests that perioperative administration is efficacious for postoperative analgesia, preoperative anxiolysis, attenuation of the haemodynamic response to laryngoscopy and intubation, and preventing chronic post-surgical pain, postoperative nausea and vomiting, and delirium. This article reviews the clinical trial data describing the efficacy and safety of gabapentin in the setting of perioperative anaesthetic management.

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Gabapentin was introduced in 1993 as an adjuvant anticonvulsant drug for the treatment of refractory partial seizures. Subsequently, it was shown to be effective in treating a variety of chronic pain conditions, including post-herpetic neuralgia, diabetic neuropathy, complex regional pain syndrome, inflammatory pain, central pain, malignant pain, trigeminal neuralgia, HIV-related neuropathy, and headaches.^{5 23 40 43 64 73 92 93 129} In 2002, gabapentin was approved by the US Food and Drug Administration for the treatment of post-herpetic neuralgia. In the UK, gabapentin has a full product licence for treatment of all types of neuropathic pain.

Gabapentin use has more recently extended into the management of more acute conditions, particularly in the perioperative period. More than 30 clinical trials evaluating the potential roles of gabapentin for postoperative analgesia, preoperative anxiolysis, prevention of chronic post-surgical pain, attenuation of haemodynamic response to direct laryngoscopy and intubation, prevention of postoperative nausea and vomiting (PONV), and postoperative delirium have been published within the last 5 yr. These studies reflect many important areas of anaesthesia research and it is interesting that a single drug may have multimodal effects. In this review, various aspects of these perioperative applications will be discussed after a brief description of gabapentin's pharmacology and anti-nociceptive mechanisms.

Pharmacology and anti-nociceptive mechanisms

Chemistry, pharmacokinetics, and adverse effects

Gabapentin, 1-(aminomethyl)cyclohexane acetic acid, is a structural analogue of the neurotransmitter γ -aminobutyric

acid (GABA) (Fig. 1) with a molecular formula of $C_9H_{17}NO_2$ and a molecular weight of 171.24. It is a white crystalline solid, which is highly charged at physiological pH, existing as a zwitterion with a pK_{a1} of 3.7 and a pK_{a2} of 10.7. It is freely soluble in water in both basic and acidic aqueous solutions. High performance liquid chromatography⁴⁴ and gas chromatography⁴⁶ can be used for drug assay in plasma and urine.

The absorption of gabapentin is dose-dependent due to a saturable L-amino acid transport mechanism in the intestine.¹⁰¹ Thus, the oral bioavailability varies inversely with dose. After a single dose of 300 or 600 mg, bioavailability was approximately 60% and 40%, respectively.^{120 125} Plasma concentrations are proportional with dose up to 1800 mg daily and then plateau at approximately 3600 mg daily.¹⁰⁹ Gabapentin is extensively distributed in human tissues and fluid after administration. It is not bound to plasma proteins¹²⁴ and has a volume of distribution of 0.6–0.8 litre kg^{-1} .^{88 125} It is highly ionized at physiological pH; therefore, concentrations in adipose tissue are low.¹²⁴ After ingestion of a single 300 mg capsule, peak plasma concentrations (C_{max}) of 2.7 $\mu g\ ml^{-1}$ are achieved within 2–3 h.^{120 126} Concentrations of gabapentin in cerebrospinal fluid are approximately 5–35% of those in plasma, whereas concentrations in brain tissue are approximately 80% of those in plasma.^{8 9 77}

In humans, gabapentin is not metabolized¹²⁷ and does not induce hepatic microsomal enzymes.⁹⁶ It is eliminated unchanged in the urine and any unabsorbed drug is excreted in the faeces.¹²⁴ Elimination rate constant, plasma clearance, and renal clearance are linearly related to creatinine clearance.^{17 88 127} Therefore, dose adjustment is

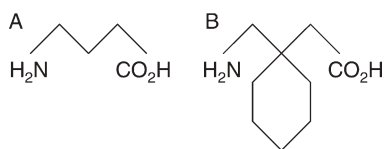


Fig 1 The structural formulae of GABA (A) and gabapentin (B).

necessary in patients with compromised renal function. In patients with normal renal function, the elimination half-life of gabapentin when administered as monotherapy is between 4.8 and 8.7 h.⁹¹ Gabapentin is removed by haemodialysis, and a maintenance dose after each treatment should provide steady-state plasma concentrations comparable with those attained in patients with normal renal function.¹³⁰ No clinically significant interactions between gabapentin and drugs excreted predominantly by renal mechanisms have been reported. Cimetidine, a H₂ receptor blocker, decreases the renal clearance of gabapentin by 12% when administered concomitantly,⁸⁸ and antacids¹³ reduce the bioavailability of gabapentin from 10% (when given 2 h before gabapentin) to 20% (when given concurrently or 2 h after gabapentin) in healthy individuals.

Gabapentin is generally well tolerated with a favourable side-effect profile. When the safety and tolerability of gabapentin were evaluated⁶³ in 2216 patients undergoing seizure treatment, reported adverse effects were somnolence (15.2%), dizziness (10.9%), asthenia (6%), headache (4.8%), nausea (3.2%), ataxia (2.6%), weight gain (2.6%), and amblyopia (2.1%). Similar side-effects were observed in patients with chronic pain treated with gabapentin.^{5 93}

Anti-nociceptive mechanisms

A number of mechanisms may be involved in the actions of gabapentin.¹² Possible pharmacologic targets of gabapentin are selective activation of the heterodimeric GABA_B receptors which consist of GABA_{B1a} and GABA_{B2} subunits;^{10 72} enhancement of the *N*-methyl-D-aspartate (NMDA) current at GABAergic interneurons;⁴¹ blocking α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor mediated transmission in the spinal cord;^{14 98} binding to the L- α -amino acid transporter;^{37 103} activating adenosine triphosphate sensitive K⁺ (K_{ATP}) channels;^{35 69} activating hyperpolarization-activated cation current (I_h) channels;^{104 105} and modulating Ca²⁺ current by selectively binding to [³H]gabapentin (a radioligand), the $\alpha_2\delta$ subunit of voltage-dependent Ca²⁺ channels (VGCCs).^{33 36 61 99} Currently, VGCC is the most likely anti-nociceptive target of gabapentin. The proposed consequence of gabapentin binding to the $\alpha_2\delta$ subunit is a reduction in neurotransmitter release and hence a decrease in neuronal hyperexcitability. Gabapentin has been shown to inhibit the evoked release of glutamate,¹⁵ aspartate,³¹ substance P, and calcitonin gene-related peptide (CGRP)³⁰ from the spinal cord of rats. Interestingly, recent studies have demonstrated that the descending noradrenergic system, spinal α_2 adrenergic

receptors and an intact spino-bulbo-spinal circuit are crucial elements influencing the analgesic effects of gabapentin in addition to $\alpha_2\delta$ interaction.^{106 107}

Postoperative analgesia

Postoperative pain is not purely nociceptive in nature, and may consist of inflammatory, neurogenic, and visceral components. Therefore, multimodal analgesic techniques utilizing a number of drugs acting on different analgesic mechanisms are becoming increasingly popular.¹¹ Gabapentin may have a role to play in this area and within the past 5 yr, there have been more than 20 well-conducted, randomized controlled trials using perioperative gabapentin as part of a multimodal postoperative analgesic regimen.

Systematic review and meta-analyses

A systematic review of randomized clinical trials of gabapentin and pregabalin for acute postoperative pain relief¹⁸ involving a total of 663 patients from seven original randomized placebo-controlled trials, when the patients from the pregabalin studies were excluded (Table 1).^{20 22 25 79 90 114 115} There were 333 subjects who received oral gabapentin and 330 who received placebo. Three outcome measures (postoperative opioid requirements, pain score at rest, and pain score during activity) were compared between gabapentin and placebo groups. Gabapentin significantly reduced postoperative opioid requirement during the first 24 h in six of the seven studies. The mean pain scores at rest and during activity, within 6 h after surgery, were significantly reduced in three of seven and two of four studies, respectively.

A meta-analysis⁹⁷ of 719 patients from eight original randomized controlled trials addressed the role of gabapentin in acute postoperative pain management.^{20 22 25 79 80 90 114 115} seven of which had been covered in the previously discussed systematic review. There were 361 subjects who received oral gabapentin and 358 who received placebo. Side-effects from analgesia or gabapentin were analysed for the first time, in addition to total analgesic consumption, pain scores at rest or on mobilization in the first 24 h after surgery. Their pooled analysis demonstrated no significant differences with respect to the incidence of opioid or gabapentin-related adverse effects between the groups, whereas preoperative gabapentin was effective in reducing postoperative opioid consumption [weighted mean differences (WMD) 13.7, 95% confidence interval (CI) 8.9–18.5] and pain scores (WMD 9.0, 95% CI 8.1–9.9 for pain at rest; WMD 11.0, 95% CI 6.7–15.3 for pain with mobilization).

The analgesic effect of perioperative gabapentin⁴⁷ was evaluated in a meta-analysis of 896 patients from 12 randomized controlled trials.^{20 22 25 38 66 79–81 90 114–116} Eight of these had been included in the previously discussed meta-analysis. There were 449 subjects who received oral gabapentin and 447 who received placebo. Side-effects,

Table 1 Perioperative randomized placebo-controlled trials of gabapentin included in major systematic review/meta-analyses. G, gabapentin group; Intraop, during surgery; P, Placebo; Postop, after surgery; Preop, before surgery; NM, not measured; NS, statistically not significant; *Opioid sparing is the cumulative opioid consumption up to 24 h post-surgery. TA, treatment arms; *P*-values indicate favourable effects for gabapentin group unless otherwise specified

Reference	Procedure	Subjects, G/P (at final analysis)	Single vs multiple dose	Dose (mg)/timing	Outcome 1: Pain score reduction	Outcome 2: *Opioid sparing	Side-effects	Jadad score
21	Abdominal hysterectomy	39/32	Multiple	1200/1 h Preop, then 600 tid for 24 h	NS	<i>P</i> <0.001	NS	5
22	Radical mastectomy	31/34	Single	1200/ 1 h Preop	Pain at rest: NS; pain on movement: <i>P</i> <0.02	<i>P</i> <0.0001	NS	5
25	Modified radical mastectomy or lumpectomy with axillary dissection	22/24	Multiple	400/tid Preop till Postop day 10	NS	NS	NM	4
39	Abdominal hysterectomy	23/24	Multiple	600/1 h Preop, then tid till Postop day 2	<i>P</i> <0.05	<i>P</i> <0.05	G: more sedation <i>P</i> =0.045	5
66	Arthroscopic anterior cruciate ligament repair	20/20	Single	1200/1–2 h Preop	NS	<i>P</i> <0.001	NS	5
79	Laparoscopic cholecystectomy	153/153	Single	300/2 h Preop	<i>P</i> <0.05	<i>P</i> <0.05	G: more sedation and nausea/retching/vomiting <i>P</i> <0.05	3
80	Lumbar discectomy	28/28	Single	300/2 h Preop	<i>P</i> <0.05	<i>P</i> <0.05	NS	4
81	Lumbar discectomy	80 (4 TA)/20	Single	300 or 600 or 900 or 1200/2 h Preop	<i>P</i> <0.05	<i>P</i> <0.05	NS	5
82	Open donor nephrectomy	40 (2 TA)/20	Single	600/2 h Preop or 600/post-incision	<i>P</i> <0.05	<i>P</i> <0.05	NS	5
86	Lumbar laminectomy and discectomy	30/30	Multiple	400/night before surgery, then 400/2 h Preop	NS	NS	NS	4
90	Vaginal hysterectomy	38/37	Single	1200/2.5 h Preop	NS	<i>P</i> =0.005	NS	5
113	Major orthopaedic surgery	30 (2 TA)/15	Single	800 or 1200/1 h Preop	NS	<i>P</i> <0.05	NS	1
114	Lumbar discectomy or spinal fusion surgery	25/25	Single	1200/1 h Preop	<i>P</i> <0.01 (only up to Postop 4 h); NS at Postop 24 h	<i>P</i> <0.001	G: less vomiting and urinary retention <i>P</i> <0.05	5
115	Abdominal hysterectomy	25/25	Single	1200/1 h Preop	<i>P</i> <0.001	<i>P</i> <0.001	NS	5
116	Rhinoplasty or endoscopic sinus surgery	25/25	Single	1200/1 h Preop	<i>P</i> <0.01	Less Intraop fentanyl consumption <i>P</i> <0.05 and Postop diclofenac usage <i>P</i> <0.001	G: more dizziness <i>P</i> <0.05	5
117	Abdominal hysterectomy	25/25	Multiple	1200/1 h Preop, then daily at 09:00 for 2 days	<i>P</i> <0.05	<i>P</i> <0.05	NS	5

postoperative pain scores, and analgesic use were analysed according to the treatment condition. They found that gabapentin administration was associated with a significantly higher incidence of sedation [odds ratio (OR) 3.28, 95% CI 1.21–8.87]. Perioperative gabapentin was associated with significant decreases in postoperative pain scores (WMD 1.57, 95% CI 0.99–2.14 at 0–4 h after surgery; WMD 0.74, 95% CI 0.45–1.03 at 20–24 h after surgery) and opioid consumption (WMD 17.84, 95% CI 12.18–23.5).

The efficacy and tolerability of pre- and postoperative gabapentin administration for the control of acute

postoperative pain was evaluated in a meta-analysis⁴⁵ of 1151 patients from 16 randomized controlled trials,^{20 22 25 38 66 79–82 86 90 113–117} of whom 614 received gabapentin. This is by far the most comprehensive meta-analysis including the highest number of original studies on this topic. Pain intensity, total analgesic consumption, time to first request for rescue analgesia, and adverse effects were analysed separately in three subgroups: a group receiving a single dose of gabapentin 1200 mg before operation, a group receiving a single dose of gabapentin of <1200 mg, and a group receiving multiple doses of gabapentin in the perioperative period. A single preoperative dose of

gabapentin 1200 mg or less, but not multiple perioperative doses, significantly decreased the pain intensity at 6 and 24 h after operation [at 6 h: WMD 16.55, 95% CI 7.44–25.66 (1200 mg gabapentin) and WMD 22.43, 95% CI 17.19–27.66 (<1200 mg gabapentin); at 24 h: WMD 10.87, 95% CI 0.84–20.90 (1200 mg gabapentin) and WMD 13.18, 95% CI 6.68–19.68 (<1200 mg gabapentin)]. Twenty-four hour cumulative opioid consumption was significantly reduced in all three subgroups [WMD 27.9, 95% CI 24.29–31.52 (1200 mg gabapentin); WMD 15.98, 95% CI 8.5–23.45 (<1200 mg gabapentin); 24% reduction in patient-controlled analgesia (PCA) morphine usage (multiple doses gabapentin)]. Time to first request for rescue analgesia was not frequently reported in the included studies: two studies of 1200 mg gabapentin showed a statistically significant delay (WMD 7.42, 95% CI 0.49–14.34), no study reported in the <1200 mg gabapentin group, and one study reported no difference in the multiple dose group. Pooled data on adverse effects from all studies revealed that gabapentin was associated with more sedation (Peto OR 3.86, 95% CI 2.5–5.94), but less vomiting (Peto OR 0.58, 95% CI 0.39–0.86) and pruritis (Peto OR 0.27, 95% CI 0.1–0.74) compared with control.

Double blind, randomized placebo controlled trials

The effects of perioperative gabapentin on postoperative pain control have been evaluated in 27 studies: seven performed in patients undergoing abdominal hysterectomy, four in spinal surgery, three in breast surgery, two in laparoscopic surgery, two in arthroscopic surgery, two in ear-nose-throat surgery, and seven in patients having other surgical procedures (Tables 1 and 2). These clinical trials covered the whole spectrum of anaesthetic techniques: monitored anaesthesia care,¹¹⁶ regional block,² neuraxial block,¹¹⁸ i.v. regional anaesthesia,¹¹⁹ and general anaesthesia were included. The influence of perioperative gabapentin on postoperative analgesia, as measured by pain scores and opioid consumption, is mostly favourable.

The efficacy of gabapentin in postoperative analgesia has been shown in good-quality studies in various clinical situations. Nevertheless, two major practical issues were not adequately addressed, dose–response relationship and cost-effectiveness. In order to utilize gabapentin efficiently, further investigations should focus on its dose–response relationship. Acute pain from different surgical insults may have different neuropathic components; hence, dose regimen could be surgery-specific. Introducing gabapentin in the perioperative setting has a potential economic impact on the health-care system because the drug is relatively expensive and the population involved is huge.

In summary, gabapentin given as multiple doses perioperatively offers no additional benefit in terms of pain reduction and opioid sparing when compared with a single

preoperative dose. Practically speaking, gabapentin in a single dose of 1200 mg or less is recommended considering the potential risk of adverse effects.

Pre-emptive analgesia

Only one study has investigated the possible pre-emptive analgesic effect of gabapentin⁸² and it showed that gabapentin given 2 h before surgery had no benefit over post-incision administration (through a nasogastric tube after surgical incision) in terms of pain scores and fentanyl consumption in patients undergoing open donor nephrectomy.

Physiological recovery after surgery

Gabapentin appears to have indirect beneficial effects on physiological recovery after surgery secondary to optimal pain management. Perioperative gabapentin significantly improved postoperative peak expiratory flow rate (PEFR) compared with placebo on postoperative days 1 and 2 ($P=0.002$) after abdominal hysterectomy.³⁸ Perioperative gabapentin significantly improved forced vital capacity (FVC) and PEFR at 24 h ($P=0.005$; $P=0.024$) and 48 h ($P=0.005$; $P=0.029$) after thoracotomy.⁷⁸ Oxygen saturation at 24 h after abdominal hysterectomy was significantly higher in patients having preoperative gabapentin when compared with placebo ($P<0.05$).²⁴ Gabapentin appears to enhance recovery of bowel function after lower abdominal surgery. Passage of flatus, return of bowel function, and resumption of oral dietary intake occurred earlier after abdominal hysterectomy in patients receiving gabapentin compared with placebo ($P<0.001$).¹¹⁷ Preoperative gabapentin also improved early postoperative knee mobilization (especially flexion) after arthroscopic anterior cruciate ligament repair ($P<0.05$).⁶⁶

Preoperative anxiety

Gabapentin decreases preoperative anxiety. Although 1200 mg gabapentin was less effective in relieving preoperative anxiety than 15 mg oxazepam,⁹⁰ significantly lower preoperative visual analogue scale (VAS) anxiety scores ($P<0.0001$) have been demonstrated in patients with gabapentin, compared with placebo, premedication before knee surgery.⁶⁶

Prevention of chronic post-surgical pain

Chronic post-surgical pain (CPSP) is a complex bio-psycho-social phenomenon with enormous economic impact. It is defined as persistent pain, which has developed after a surgical procedure, of at least 2 months duration, where other causes such as continuing malignancy or chronic infection have been excluded.⁵⁹ CPSP is particularly common after amputation,⁷⁴ inguinal hernia

Table 2 Randomized placebo-controlled trials of gabapentin (not included in Table 1) on perioperative analgesia. D, day; EMLA, eutectic mixture of anaesthetics; G, gabapentin; MN, midnight; P, placebo; PCEA, patient-controlled epidural analgesia; Postop, after surgery; Preop, before surgery; VAS, visual analogue scale

Reference	Procedure	Subjects (at final analysis), G/P	Dose (mg)/timing	Outcomes	Jadad score
2	Arthroscopic shoulder surgery	27/26	800/2 h Preop	No augmentation of postoperative analgesia (pain scores, first Postop request for analgesia, and oral analgesic consumption) in patients given interscalene brachial plexus blocks	5
3	Thyroidectomy	37/35	1200/2 h Preop	G: lower pain scores at rest and during swallowing ($P<0.01$), less total morphine consumption ($P<0.001$) within 24 h Postop	5
6	Laparoscopic sterilization	38/38	1200/30 min Preop	G: smaller number of patients requesting morphine ($P=0.049$) within 4 h Postop	5
24	Abdominal hysterectomy	25/25+25 (G and acetaminophen)	1200/1 h Preop	G vs P at 24 h Postop ($P<0.05$): lower pain scores at rest and at movement, less morphine consumption, better oxygen saturation, and lower patient dissatisfaction scores G and acetaminophen vs G at 24 h Postop: further reduction in morphine consumption ($P<0.05$)	5
26	Breast surgery for cancer	23 (with EMLA+ropivacaine)/23	400/six hourly from Preop evening 18:00 till Postop D8	Multimodal analgesia with gabapentin and local anaesthetics reduced acute (acetaminophen and opioid consumption, time to first analgesia; $P<0.02$) and chronic pain at 3 months Postop ($P=0.028$)	5
27	Abdominal hysterectomy	27 (with ropivacaine)/24	400/six hourly from Preop MN till Postop D7	G (with ropivacaine): reduced opioid consumption after surgery till Postop D7 ($P<0.02$), fewer patients experienced pain at 1 month Postop ($P=0.045$)	3
29	Abdominal hysterectomy	25/28	400/six hourly from 18 h Preop till Postop D5	G: no effect on acute postoperative pain; significant reduction in the incidence ($P=0.002$) and intensity ($P=0.003$) of pain at 1 month Postop	3
67	Tonsillectomy	22/27	1200/1 h Preop, 2×600 on operation D, 3×600 for the next 5 D	G: less ketobemidone consumption ($P=0.003$) 0–24 h Postop; more dizziness ($P=0.002$), gait disturbance ($P=0.02$), and vomiting ($P=0.046$) during Postop D 0–5	5
78	Thoracotomy for lobectomy	25/25	1200/1 h Preop	G: lower pain scores at rest and after coughing ($P<0.05$), reduced morphine consumption ($P=0.005$), better lung function (FVC and PEFR) ($P=0.005$) within 48 h Postop, less vomiting and urinary retention ($P<0.05$)	5
118	Lower extremity surgery	20/20	1200/1 h Preop, then daily till Postop D2	G: lower pain scores 0–16 h Postop; less PCEA bolus requirement ($P<0.05$) and acetaminophen consumption ($P<0.05$), better patient satisfaction ($P<0.001$) 0–72 h Postop; more dizziness ($P<0.05$)	5
119	Hand surgery	20/20	1200/1 h Preop	<i>During surgery</i> G ($P<0.05$): lower VAS scores for tourniquet pain from 30–60 min after tourniquet inflation, prolonged time to intraoperative fentanyl rescue, reduced supplemental fentanyl requirement during surgery, better quality of anaesthesia <i>After surgery</i> G ($P<0.05$): prolonged time to first Postop analgesic request, lower VAS scores at both 1 and 2 h Postop, decreased Postop diclofenac consumption	5

repair,⁸⁵ breast surgery,⁵¹ and thoracotomy.³⁹ Surgery contributed to the development of chronic pain in approximately 20% of patients attending pain management clinics in Northern Britain.¹⁹ In Canada, there were an estimated 72 000 new cases of CPSP between 1999 and 2000.¹²²

CPSP has inflammatory¹ and neuropathic⁶⁸ components, involving peripheral and central sensitization¹³¹ that arises in response to tissue and nerve injury. Up-regulation of the $\alpha_2\delta$ subunit of VGCCs, which is a binding site for gabapentin,⁵⁸ is involved in nerve injury-induced central sensitization.⁵⁶ Because of this and since gabapentin is effective across a wide spectrum of pain states,⁹¹ its efficacy in the prevention of chronic post-surgical pain has been investigated.

Perkins and Kehlet⁸⁴ proposed that studies of CPSP should ideally include: (i) sufficient preoperative data (assessment of pain, physiologic and psychologic risk

factors for chronic pain); (ii) detailed descriptions of the operative approaches used (location and length of incisions, handling of nerves and muscles); (iii) the intensity and character of acute postoperative pain and its management; (iv) follow-up at intervals up to 1 yr or more; (v) information about postoperative interventions, such as radiation therapy or chemotherapy, that may influence pain; and (vi) long-term assessment using a standardized algorithm, including quantitative and descriptive pain assessments. From 2002 to 2006, there were four randomized controlled trials using perioperative gabapentin to prevent chronic pain after amputation, breast, and abdominal surgeries. Three studied chronic pain only as part of a broader investigation (Table 3), and one study was designed specifically to investigate the incidence of chronic pain after surgery.

Table 3 Randomized placebo-controlled trials of gabapentin for the prevention of CPSP as a secondary outcome. Postop, after surgery; Preop, before surgery

Reference	Surgical procedure	Interventions (vs control)	Subjects (at chronic pain analysis)	Dose (mg)/timing	CPSP-related outcomes	Jadad score
25	Modified radical mastectomy or lumpectomy with axillary dissection	Gabapentin, mexiletine	Gabapentin: 22, mexiletine: 20, control: 24	400/eight hourly Preop till Postop day 10	The incidence of burning pain 3 months after operation was significantly decreased in patients receiving either gabapentin or mexiletine ($P=0.003$) Gabapentin has no effect on the incidence of overall chronic pain, its intensity, or the need for analgesics 3 months after surgery	4
26	Modified radical mastectomy or lumpectomy with axillary dissection	Multimodal analgesia regimen consisting of gabapentin, an eutectic mixture of local anaesthetics (EMLA [®]) cream, and ropivacaine wound infiltration	3 months after operation Treatment: 22, control: 22 6 months after operation Treatment: 20, control: 21	400/six hourly from Preop evening 18:00 till Postop day 8	The incidence of chronic pain ($P=0.028$), and the number of patients requiring analgesics ($P=0.048$) during the first 3 months before operation were significantly reduced Multimodal analgesia regimen has no effect on the incidence of chronic pain 6 months after surgery	5
117	Abdominal hysterectomy	Gabapentin, rofecoxib, gabapentin and rofecoxib	Gabapentin: 25, rofecoxib: 25, gabapentin and rofecoxib: 25, control: 25	1200/1 h Preop, then daily at 09:00 for 2 days	The incidences of incisional pain (4–8%) at the 3 month follow-up evaluation were similar in all groups	5

Nikolajsen and colleagues⁷⁵ studied the effect of gabapentin, started immediately after surgery and continued for 30 days, on post-amputation pain in 46 patients undergoing lower limb amputation because of peripheral vascular disease. They were randomized to receive gabapentin or placebo. A 30-day treatment, in three divided doses daily, was started on the first postoperative day. The dose of gabapentin was gradually increased from 300 mg on the first day, to 2400 mg on days 13–30, with adjustment in patients with renal impairment. Only 33 patients completed the 6 month trial period and the number of dropouts was approximately the same in both groups with two in each attributed to adverse events. Gabapentin administration did not reduce the incidence or intensity of post-amputation stump and phantom pain.

The Jadad⁵⁰ scores (Table 4) of these randomized clinical trials range from 3 to 5. In general, limitations were small sample size, inadequate power to evaluate chronic pain, high dropout rate, arbitrarily chosen dosage of gabapentin, and lack of a clear definition of CPSP. None of the above studies was of sufficient methodological quality to make a conclusion on the effectiveness of gabapentin in preventing CPSP. It is also important to remember that prolonged administration of gabapentin for the prevention of CPSP, especially at high doses, is not without risk and there is a well-recognized withdrawal syndrome on discontinuation.

Gabapentin withdrawal syndrome

Abrupt discontinuation of high-dose gabapentin may cause withdrawal symptoms.⁷⁶ Clinically, it resembles alcohol or benzodiazepine withdrawal, perhaps due to a similar mechanism of action. Patients exhibit irritability, agitation,

anxiety, palpitation, and diaphoresis within 1–2 days. A patient with chronic back pain developed generalized seizures and status epilepticus secondary to gabapentin withdrawal.⁷ Therefore, tapering should always be adopted, especially for those patients taking larger doses. However, withdrawal syndrome can still rarely occur even in the presence of dose tapering.¹¹²

Attenuation of haemodynamic response to laryngoscopy and endotracheal intubation

The pressor response of tachycardia and hypertension to laryngoscopy and endotracheal intubation may increase perioperative morbidity and mortality, particularly for those patients with cardiovascular or cerebral disease.^{94 111} A variety of drugs have been used to control this haemodynamic response.⁵³ Recently, gabapentin was effective in two randomized controlled trials.

In a randomized placebo-controlled trial of 46 patients undergoing abdominal hysterectomy for benign disease,²⁸ the effect of gabapentin 1600 mg (in four divided doses, at 6 h intervals starting the day before surgery) on attenuating the pressor response was studied. Gabapentin-treated patients had significantly lower systolic ($P<0.004$) and diastolic arterial pressure ($P<0.004$) during the first 10 min after endotracheal intubation when compared with placebo. Nevertheless, gabapentin had no effect on heart rate changes. None of the patients in the gabapentin group exhibited severe hypotension when compared with the control group. Another study⁶⁵ examined the effects of a single dose of gabapentin 400 or 800 mg, given 1 h before surgery, on reducing the cardiovascular responses. Ninety patients undergoing various elective surgical procedures

Table 4 Jadad score calculation (from 0 to 5)

Items (based on randomization, blinding, and dropout)	Score, Yes/No
<i>Positive indicators of good methodological quality (mark-gaining)</i>	
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	1/0
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc.)?	1/0
Was the study described as double blind?	1/0
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc.)?	1/0
Was there a description of withdrawals and dropouts?	1/0
<i>Negative indicators of poor methodological quality (mark-losing)</i>	
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)	0/−1
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g. comparison of tablet vs injection with no double dummy)	0/−1

were divided into three groups (gabapentin in different doses and placebo). Patients receiving 800 mg of gabapentin had significantly decreased mean arterial pressure and heart rate during the first 10 min after endotracheal intubation compared with either 400 mg gabapentin or placebo ($P<0.05$).

Overall, it appears that preoperative gabapentin blunts the hypertensive response to intubation. Single and multiple doses have comparable haemodynamic effects. However, the effects may be dose-dependent and the changes in heart rate are inconsistent. Although both studies have high Jadad scores (3 or above), there are a few major limitations. Stress mediators were not measured and potential confounding factors were the variable duration of laryngoscopy and different agents for maintenance of anaesthesia. None of them recorded the duration of each intubation. Arterial pressure and heart rate responses have been shown to be greater when the duration of laryngoscopy exceeds 30 s.¹⁰² It appears that the maximum increase in arterial pressure occurs with laryngoscopy and the maximum increase in heart rate occurs with endotracheal intubation.³² Sevoflurane/nitrous oxide/oxygen were used in one study and maintenance agents were not specified in the other. Arterial baroreflex function is known to be significantly depressed during sevoflurane and nitrous oxide anaesthesia.¹⁰⁸ The mechanism of gabapentin in controlling this haemodynamic response remains unknown. Since gabapentin inhibits membrane VGCCs, it is possible that it may have a similar action to calcium channel blockers.⁹⁵ There is, as yet, no data, on the possible role of gabapentin in the attenuation of other aspects of the stress response to surgery.

Prevention of PONV

PONV are common after anaesthesia and surgery with an overall incidence of 25–30%.^{16 71 128} It is also one of the

most common reasons for poor patient satisfaction ratings in the postoperative period.⁷⁰ Gabapentin has been shown to be useful in reducing chemotherapy-induced nausea in an open label preliminary study.⁴² Mitigation of tachykinin neurotransmitter activity by gabapentin has been a postulated mechanism. Recently, the potential anti-emetic effect of gabapentin was evaluated in the perioperative setting.

A study of 250 patients⁸³ undergoing elective laparoscopic cholecystectomy who received either a single dose of 600 mg gabapentin or placebo 2 h before the operation found that the patients receiving gabapentin had a significantly lower incidence of PONV (37.8% vs 60%; $P=0.04$) and postoperative fentanyl patient-controlled analgesia requirements [221.2 (92.40) vs 505.9 (82.0) μg ; $P=0.01$] for 24 h. The incidence of side-effects in both the groups was similar. The severity of PONV was graded from mild to severe. Patients with PONV, despite preoperative gabapentin (46/125 in the treatment group), had a similar severity grading to those in the placebo group. To our knowledge, this is the only clinical trial evaluating the potential of gabapentin in the prevention of PONV. Other perioperative studies of gabapentin have measured PONV as a secondary outcome and some found significant effects (Table 5). The methodological quality of this study was good with a Jadad score of 5. Both study groups were comparable with regard to the risk of suffering PONV. Anaesthetic techniques and postoperative pain management protocol were standardized. The mechanism of gabapentin in the prevention of PONV is unknown but it could possibly be due to the indirect effect of opioid sparing or a direct effect on tachykinin activity.⁶⁰ A tendency towards a lower incidence of PONV in patients treated with gabapentin, although statistically insignificant, was noted in several studies on postoperative analgesic effects of gabapentin.^{3 24 90}

Reduction of postoperative delirium

Perioperative delirium complicates hospital stay for more than 2 million elderly people every year in the USA.⁸⁹ It has been associated with poor cognitive and functional recovery, longer hospital stay, greater hospital costs,^{34 110} cognitive decline after discharge,⁵⁷ and increased overall mortality.⁴⁸ Postoperative delirium represents global brain dysfunction, which is a multifactorial syndrome resulting from the complex interaction of predisposing and precipitating factors related to the patient, anaesthesia, and surgery.⁴ Currently, primary prevention is probably the most effective approach.⁴⁹ Postoperative pain and pain management strategies are independently associated with the development of delirium.¹²³ Leung and colleagues⁵⁵ investigated the effect of gabapentin on reducing the incidence of postoperative delirium in 21 patients having spinal surgery who were randomized to receive either gabapentin or placebo. There was significantly less

Table 5 Perioperative gabapentin and its effect on PONV

Reference	Procedure	Subjects (at final analysis), gabapentin/placebo	Dose (mg)/timing	PONV	Jadad score
67	Tonsillectomy	22/27	1200/1 h before surgery, 2×600 on operation day, 3×600 for the next 5 days	Less vomiting ($P=0.046$) during postoperative days 0–5	5
78	Thoracotomy for lobectomy	25/25	1200/1 h before surgery	Less vomiting within 48 h after surgery ($P<0.05$)	5
79	Laparoscopic cholecystectomy	153/153	300/2 h before surgery	More nausea/retching/ vomiting within 24 h after surgery ($P<0.05$)	3
114	Lumbar discectomy or spinal fusion surgery	25/25	1200/1 h before surgery	Less vomiting within 24 h after surgery ($P<0.05$)	5

delirium in patients having perioperative gabapentin (0/9=0% vs 5/12=42%, $P=0.045$), in the dose of 900 mg started 1–2 h before surgery and continued for the first 3 postoperative days. No specific side-effects were associated with gabapentin administration.

The mechanism of gabapentin reducing postoperative delirium is unknown. It could possibly be related to its opioid sparing effect. Although the study had a high Jadad score of 5, a small sample size (only nine patients in the gabapentin group) with no power analysis and the recruitment of only patients undergoing spinal surgery are pitfalls of this pilot study. The incidence of delirium [5/12 patients (42%) who received placebo] in this study may be an overestimation as the incidence in a much larger group of 341 patients after spinal surgery was 12.5% in patients >70 yr old⁵² and one would expect it to be even less common in younger patients. Another limitation was that the assessment of delirium was focused only on the early postoperative period and, therefore, the incidence of later onset delirium may have been missed. The efficacy of gabapentin for this indication should be further investigated through well-conducted double blind, randomized clinical trials.

Conclusion

All perioperative applications of gabapentin are ‘off-label’. ‘Off-label’ prescription is the use of drugs outside the terms of their licence in clinical practice. It is different from the prescription of unlicensed drugs which are products that have no licence for any clinical situation or maybe in the process of evaluation leading to such a licence. The clinical decision to prescribe medicines for unapproved indications should be ideally based on professional judgement in terms of safety, quality, and efficacy. According to a recent survey in the USA, gabapentin had the highest proportion of off-label prescription (83%) among 160 commonly prescribed drugs; where only less than 20% of its off-label use had strong scientific evidence of clinical efficacy.⁸⁷

Gabapentin drew substantial media attention, because its manufacturer was investigated and convicted for

inappropriate marketing of off-label uses of the drug⁵⁴ and for inappropriate promotion of unapproved uses for gabapentin.^{100 121}

Is gabapentin a panacea for perioperative anaesthetic care? A single preoperative dose of gabapentin was useful as an adjunct for postoperative pain management. Although gabapentin has anti-hyperalgesic effects,^{21 62} there is no scientific evidence to support its use for the prevention of CPSP. The effects of gabapentin on attenuating haemodynamic response to tracheal intubation, preventing PONV, and reducing postoperative delirium are promising but, as yet, inconclusive and more studies are expected in the near future. Gabapentin, as a potential multimodal perioperative drug, could be given in the dose of 900 mg 1–2 h before surgery.

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