Regional Anesthesia And Pain

Review article: The role of anticonvulsant drugs in postoperative pain management: a bench-to-bedside perspective

[Le rôle des anticonvulsivants dans le traitement de la douleur postopératoire : perspective d'une application]

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Purpose: Anticonvulsant drugs are effective in the treatment of chronic neuropathic pain but were not, until recently, thought to be useful in more acute conditions such as postoperative pain. However, similar to nerve injury, surgical tissue injury is known to produce neuroplastic changes leading to spinal sensitization and the expression of stimulus-evoked hyperalgesia and allodynia. Pharmacological effects of anticonvulsant drugs which may be important in the modulation of these postoperative neural changes include suppression of sodium channel, calcium channel and glutamate receptor activity at peripheral, spinal and supraspinal sites. The purpose of this article is to review preclinical evidence and clinical trial data describing the efficacy and safety of anticonvulsant drugs in the setting of postoperative pain management.

Source: A Medline search was performed to retrieve available literature on the basic and clinical pharmacology of anticonvulsant drugs as they pertain to postoperative pain management.

Principal findings: Numerous laboratory studies have described analgesic effects of different anticonvulsant drugs in experimental pain models. Furthermore, several recent clinical trials have shown that anticonvulsants may reduce spontaneous and movement-evoked pain, as well as decrease opioid requirements postoperatively. Some early findings suggest further that anticonvulsant drugs may alleviate postoperative anxiety, accelerate postoperative functional recovery and reduce chronic postsurgical pain.

Conclusion: Given the incomplete efficacy of currently available non-opioid analgesics, and the identified benefits of opioid sparing, anticonvulsant medications may be useful adjuncts for postoperative analgesia. Further research in this field is warranted.

***Objectif** : Les anticonvulsivants sont efficaces contre la douleur neuropathique chronique mais, jusqu'à tout récemment, on ne les croyait pas utiles pour traiter les douleurs aiguës, comme les douleurs postopératoires. La lésion tissulaire chirurgicale, comme la lésion nerveuse, produit des modifications neuroplastiques menant à une sensibilisation rachidienne et à l'expression d'hyperalgésie et d'allodynie provoquées par un stimulus. Les effets pharmacologiques des anticonvulsivants, dont la suppression de l'activité des récepteurs du canal sodique, du canal calcique et du glutamate aux sites périphérique, rachidien et suprarachidien, peuvent être importants dans la modulation de ces changements nerveux postopératoires. Nous voulions revoir la preuve clinique et les données d'études cliniques décrivant l'efficacité et l'innocuité des anticonvulsivants pour traiter la douleur postopératoire.*

***Source** : Nous avons extrait de Medline les articles sur la pharmacologie théorique et clinique des anticonvulsivants comme traitement de la douleur postopératoire.*

***Constatations principales** : De nombreuses études de laboratoire ont décrit les effets analgésiques de différents anticonvulsivants pour des modèles de douleur expérimentaux. En outre, quelques récentes études cliniques ont montré qu'ils pouvaient réduire la douleur spontanée et provoquée par le mouvement, et aussi les besoins postopératoires d'opioïdes. Certains résultats précoces suggèrent qu'ils puissent atténuer l'anxiété postopératoire, accélérer la récupération fonctionnelle postopératoire et réduire la douleur postchirurgicale chronique.*

***Conclusion** : Étant donné l'efficacité réduite des analgésiques non opioïdes actuellement offerts et les bénéfices connus de l'économie des opioïdes, les anticonvulsivants peuvent compléter l'analgésie postopératoire. La recherche doit se poursuivre dans ce domaine.*

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Presented in part, at the 8th International Conference on the Mechanisms and Treatment of Neuropathic Pain, San Francisco, CA, USA.

Support: This work was supported by PSI Foundation Grant #03-30 and Queen's University Grant #383-861.

Accepted for publication January 5, 2006.

Revision accepted January 20, 2006.

Competing interests: None declared.

OVER 40 million surgeries per year are performed in North America, including major procedures to treat cancer, cardiovascular, traumatic and degenerative conditions.[1] Postoperative care involves pain and symptom management,[2] prevention and treatment of postoperative complications[3] and recovery of preoperative function.[4] While postoperative pain at rest has long been recognized to be responsive to opioid therapy,[5] attention has shifted over the past two decades to the understanding and treatment of movement-evoked or dynamic pain.[6] Postoperative pain evoked by movement is considerably less responsive to opioids.[5] Perhaps more importantly, poorly controlled movement-evoked pain has been related to postoperative pulmonary,[7] cardiac[8] and thromboembolic[9] complications which can be both devastating to the patient and costly to the healthcare system.[10,11]

With the early discovery that anticonvulsant drugs could be useful in treating trigeminal neuralgia,[12,13] neurophysiological concepts evolved which make some associations between epilepsy and neuropathic pain.[14] Similarly, some parallels can be drawn between postsurgical and neuropathic pain. Since stimuli which evoke pain after surgery are often mild in intensity or altogether innocuous, movement-evoked pain is actually a manifestation of hyperalgesia or allodynia.[15] This observation highlights some common pathophysiological, clinical and pharmacological features that postoperative pain shares with neuropathic pain. Although surgical nerve injury is indeed one cause of neuropathic pain, initiation mechanisms of postsurgical and neuropathic pain are usually different. However, perpetuation and maintenance of neuropathic and postsurgical pain both often involve sensitization of primary afferent and second-order dorsal horn neurons.[16,17] Furthermore, excitatory amino acids such as glutamate play a major role in both of these conditions, and both neuropathic and postsurgical pain are often manifest by hyperalgesia and allodynia at or near the affected sites.[18] There is also some overlap with respect to treatment responses. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are effective for postoperative[19,20] but not neuropathic pain[21], whereas opioids[22,23] and local anesthetics[24,25] may be helpful in both conditions. The purpose of this review is to consider and weigh emerging evidence suggesting that, as with neuropathic pain, some anticonvulsant drugs may be effective in reducing postoperative pain.

Methods

A literature search was conducted using the MEDLINE Database (1966-October 2005). The database search strategy involved a Boolean search of: (carbamazepine OR ethosuximide OR phenobarbital OR phenytoin OR primidone OR valproic OR valproate OR felbamate OR gabapentin OR lamotrigine OR levetiracetam OR oxcarbazepine OR pregabalin OR isobutylgaba OR tiagabine OR topiramate OR vigabatrin OR zonisamide OR clobazam) AND (pain OR nociceptive OR nociception OR antinociceptive OR antinociception OR analgesia OR analgesic) AND (postoperative OR operative OR operation OR surgery OR surgical OR incision OR incisional OR postincision). Selected review articles were used for the discussion of pharmacological mechanisms and selected preclinical studies involving the rat formalin pain model and other studies of interest were used for the discussion of preclinical evidence of analgesic efficacy. All published randomized controlled trials were selected for the discussion of clinical evidence.

Anticonvulsant drug mechanisms

Anticonvulsant drugs, so defined for their ability to suppress experimental and clinical seizures, have been classified as "first-generation" anticonvulsants (e.g., benzodiazepines, carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone and valproic acid) which were introduced between 1910 and 1970, and "second-generation" anticonvulsants (e.g., felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin and zonisamide) which were introduced more recently.[26] Most anticonvulsant drugs exert multiple pharmacological actions.[27] Anticonvulsant mechanisms which are likely important in the modulation of postoperative pain[28] include sodium channel blockade (e.g., with carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenytoin, topiramate and zonisamide), calcium channel blockade (e.g., with carbamazepine, ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, topiramate, valproic acid and zonisamide) and suppression of glutamate release or action on NMDA/AMPA receptors (e.g., with carbamazepine, felbamate, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, topiramate and valproic acid), (Figure 1, Table I). Although several anticonvulsant drugs potentiate the inhibitory neurotransmitter gamma-amino butyric acid (GABA) which plays a role in pain modulation,[29] analgesic effects of GABAergic anticonvulsants such as benzodiazepines and barbiturates are not reliably observed.[30,31] Most recognized anticonvulsant mechanisms involve the central nervous system and, indeed, central sensitization is important in postoperative pain.[17] However, the substantial contributions of

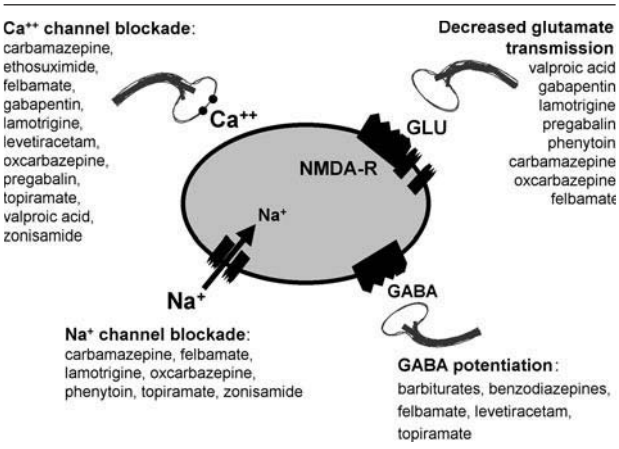

FIGURE Pharmacological mechanisms of anticonvulsant drugs. GABA= gamma-amino butyric acid; GLU = glutamate; NMDA-R = N-methyl-D-aspartate receptor.

peripheral tissue inflammation to the pathogenesis of postoperative pain warrants also the consideration of any peripheral mechanisms of anticonvulsant drugs. Of interest, the side effect of gingival hyperplasia with phenytoin has led to extensive laboratory and clinical investigations describing phenytoin's wound healing and anti-inflammatory properties due to a direct effect on tissue fibroblasts.[32] Some clinical studies have suggested that these peripheral effects of phenytoin may also contribute to pain reduction.[33,34] Peripheral effects of another anticonvulsant were reported in a laboratory study showing that, in addition to analgesia, carbamazepine demonstrates an anti-inflammatory effect as indicated by decreased plasma extravasation, possibly due to reduction of neurogenic inflammation.[35] Finally, it is interesting to observe from rat formalin pain studies, that local injections of gabapentin[36] or lamotrigine[37] exert analgesic effects, suggesting a direct action of these drugs on peripheral neurotransmission.

Preclinical evidence of analgesic efficacy

Although the clinical predictive value of many preclinical pain models is debatable, several features of the biphasic rat formalin pain response are thought to parallel changes seen after surgery.[38] While the first phase of pain behaviour following *sc* formalin injection has been equated with acute nociception during surgery, the second phase is thought to parallel later expressions of postoperative pain which are sustained by spinal sensitization and possibly by peripheral inflammation.[39] Of relevance to this review, the antinociceptive effects of several anticonvulsants have been evaluated in the rodent formalin pain model (Table I). While both phases 1 and 2 formalin-induced nociception were shown to be reduced by ethosuximide[40,41] and vigabatrin,[42] only phase 2 was reduced by carbamazepine,[43] gabapentin,[44] lamotrigine,[45] oxcarbazepine[46] and pregabalin.[44] Equivocal results were reported for tiagabine[41,45] and valproic acid,[41,47] possibly due to species differences. Finally, small numbers of studies have reported that benzodiazepines,[48,49] levetiracetam,[41] phenobarbital,[41] phenytoin,[50] topiramate[41] and zonisamide[41] were ineffective at the doses studied.

A more direct approach towards modelling postoperative pain was pursued by Brennan *et al.* using a true incisional pain model which was shown, as in humans, to result in postoperative hyperalgesia and allodynia.[51] Subsequent studies showed that the anticonvulsant, gabapentin, reduces allodynia and hyperalgesia after plantar incision[52] and thoracotomy in rat models.[53] A more recent study indicated that gabapentin alone was ineffective after rat laparotomy and induction of pancreatitis but that it did enhance opioid efficacy under these conditions.[54] Pregabalin was also shown to reduce allodynia and hyperalgesia after rat plantar incision.[52] A few human preclinical anticonvulsant studies may have relevance to postoperative pain given the nature of the experimental pain stimulus used. For example, gabapentin has been shown to reduce hyperalgesia following heat and topical capsaicin-induced sensitization[55] and also intradermal capsaicin injection[56] while hyperalgesia reduction with gabapentin after experimental first-degree burn failed to reach statistical significance.[57] In the case of lamotrigine, two studies failed to demonstrate any antihyperalgesic effect of this drug following heat and topical capsaicin-induced sensitization[58] or intradermal capsaicin injection.[59]

Anticonvulsant-opioid interactions and opioid sparing

In addition to the limited efficacy of opioids for movement-evoked pain, clinical trials have repeatedly demonstrated that opioids contribute to a wide variety of postoperative adverse effects including respiratory depression, pruritus, nausea, vomiting, ileus, urinary retention, sedation and cognitive dysfunction.[60] In fact, a recent meta-analysis has suggested that postoperative opioid sparing, following NSAID co-administration, in the range of 30–50% leads to reductions in nausea, vomiting and sedation of approximately 30%.[61] While it is unlikely that the analgesic efficacy of any currently available anticonvulsant is sufficient to eliminate the need for postoperative opioids, anti-

TABLE I Anticonvulsant drug mechanisms and analgesic efficacy in experimental pain

	Mechanism relevant to postoperative pain			*Evidence of antinociception*			
Anticonvulsant drug	*Na^+ channel blockade*	*Ca^{++} channel blockade*	*glutamate suppression*	*rodent formalin pain model*	*rodent incisional pain*	*experimental human pain*	*increased opioid effect or suppression of tolerance*
1st generation							
benzodiazepines	-	-	-	-	n/a	n/a	+
carbamazepine	++	+	+	+	n/a	n/a	+
ethosuximide	-	+	?	++	n/a	n/a	n/a
phenobarbital	-	-	-	-	n/a	n/a	n/a
phenytoin	++	?	+	-	n/a	n/a	+
primidone	-	-	-	-	n/a	n/a	n/a
valproic acid	?	+	+	-/+	n/a	n/a	+
2nd generation							
felbamate	++	+	+	n/a	n/a	n/a	+
gabapentin	?	+	+	+	+	+	+
lamotrigine	++	++	+	+	n/a	-	+
levetiracetam	-	+	?	-	n/a	n/a	n/a
oxcarbazepine	++	+	+	+	n/a	n/a	n/a
pregabalin	-	+	+	+	+	n/a	n/a
tiagabine	-	-	-	-/+	n/a	n/a	n/a
topiramate	++	+	+	-	n/a	n/a	+
vigabatrin	-	-	-	++	n/a	n/a	n/a
zonisamide	++	++	?	-	n/a	n/a	n/a

Modified from reference #27; n/a = no evidence currently available; +/- = equivocal results; ? = currently unclear whether this mechanism is involved.

convulsants may, like NSAIDs, exert an opioid sparing effect. Available evidence suggests that anticonvulsants might decrease opioid consumption either by enhancing opioid analgesia, or by suppressing mechanisms of opioid tolerance or withdrawal. For example, gabapentin has been shown to enhance opioid analgesia in both animal[62] and human[63] models of brief thermal pain as well as in animal[64] and human[65] neuropathic pain. In a cancer pain trial, phenytoin co-administration led to reduced opioid requirements and also gave better pain relief.[66] Various other lines of animal and human evidence suggest further that gabapentin,[67,68] lamotrigine,[37] topiramate,[69] carbamazepine,[70] valproic acid[71] and felbamate[72] suppress either opioid tolerance or opioid withdrawal.

Perioperative clinical trials of anticonvulsant drugs

Of all available anticonvulsant drugs, the majority of postoperative clinical trials have involved gabapentin[73–87] with single clinical trials reported for lamotrigine,[88] oxcarbazepine,[89] pregabalin[90] and valproic acid.[91]

Gabapentin

Table II includes all 15 published postoperative trials of gabapentin, listed on MEDLINE at the time of writing. All of these trials, as evaluated by the author (I.G.), received a score of at least 2 points (one each for randomization and blinding) on a three-item (1 to 5) quality scale.[92] Following various surgical procedures (Table II), gabapentin trials have involved single doses varying from 300 mg[76] to 1200 mg[73] administered from 1 to 2.5 hr before surgery. Four multidose trials studied around-the-clock gabapentin administration from one to ten days after surgery.[74,75,82,83] In all but two[75,87] of the 15 trials, rest pain and opioid consumption were significantly reduced compared to placebo. In all five trials which evaluated movement-related pain, this was also reduced compared to placebo.[73,74,80,82,83] Most studies reported no significant differences in adverse effects. However, one study reported a slightly higher incidence of sedation with gabapentin following hysterectomy[83] and Pandey *et al.* reported more sedation and nausea,[76] whereas Turan *et al.* reported less nausea/vomiting and less urinary retention with gabapentin.[79] While many different doses have been studied, Pandey *et al.* conducted a dose-response trial of gabapentin single-dose pretreatment in lumbar discectomy patients. These investigators demonstrated an analgesic ceiling effect at a dose of 600 mg, i.e., pain reduction with 600 mg was better than with 300 mg; whereas no additional

TABLE II Perioperative randomized controlled trials of gabapentin

Ref.	*Procedure*	*Single vs multidose*	*Dose (mg)*	*Control*	*n**	*Non-opioid co-analgesic*	*Pain** reduction*	*Opioid sparing*	*Adverse effects*
73	Radical Mastectomy	single	1200 1 hr pre	placebo	70	None	46-70% less movement pain @ 2 hr & 4 hr	48% less morphine	ns
74	Breast cancer surgery	multi (10 days)	400 tid	placebo mexiletine	75	acetaminophen	75% less @ rest-day 3 only; 50% less on move days 2-5 only	42% less codeine	nr
82	Breast cancer surgery	multi (8 days)	400 tid	placebo	50	topical EMLA LA infiltration	less rest and movement pain up to 8 days post	less codeine in PACU	nr
75	Abdominal hysterectomy	multi (24 hr)	1200 1 hr pre 600 tid x24 hr	placebo	80	None	ns	32% less PCA morphine	ns
80	Abdominal hysterectomy	single	1200 1 hr pre	placebo	50	None	55-65% lying; 25-40% sit	35% less PCA tramadol	ns
83	Abdominal hysterectomy	multi (72 hr)	600 tid x 72 hr from 1 hr pre	placebo rofecoxib g-r combo	110	None	17-42% less rest pain day 1; 25-32% less cough pain day 1	43% less PCA morphine	more sedation
78	Vaginal hysterectomy	single	1200 2.5 hr pre	oxazepam	75	None	17% in first 2 hr	40% less PCA fentanyl over 20 hr	ns
76	Laparoscopic cholecystectomy	single	300 2 hr pre	tramadol placebo	459	None	40-50% over 24 hr	38% less fentanyl	more sedation and nausea
77	Lumbar discectomy	single	300 2 hr pre	placebo	56	None	40% less rest pain day 0	35% less fentanyl day 0	ns
85	Lumbar discectomy	single	300, 600, 900, 1200 – 2 hr pre	placebo	100	None	less pain in all groups; significant dose-response	less fentanyl all groups; significant dose-response	ns
79	Discectomy or fusion	single	1200 1 hr pre	placebo	50	None	33-100% over 1st 4 hr	62% less PCA morphine	less vomiting *less* urinary retention
87	Lumbar laminectomy /discectomy	single	800 2 hr pre	placebo	60	None	ns	ns	ns
84	Anterior cruciate ligament repair	single	1200 1-2 hr pre	placebo	40	ketoprofen	34% less rest pain in PACU; POD 1-2 pain similar but better knee motion in gabapentin group	58% less PCA morphine	ns
81	Septoplasty	single	1200 1 hr pre	placebo	50	Diclofenac	50-60% across 24 hr	18% less fentanyl; 70% less diclofenac	more sedation
86	Donor nephrectomy	single	600 2 hr pre	placebo, g-post	60	None	33-53% less pain, pre- *vs* post ns	39% less fentanyl	ns

*Approximately equally distributed across all study treatment groups; **Refers only to gabapentin-placebo comparison and refers to pain at rest unless otherwise specified; EMLA = eutectic mixture of local anesthetics; g = gabapentin; ns = not statistically significant; nr = not reported. LA = local anagelsia; PACU = postanesthesia care unit; POD = postoperative day; PCA = patient-controlled analgesia; r = rofecoxib.

benefits were observed with doses of 900 or 1200 mg.[85] While most trials evaluated the effects of gabapentin administration before surgery, a recent trial in donor nephrectomy patients showed no difference in pain scores comparing preoperative with post-incisional administration.[86]

Three published postoperative trials have compared gabapentin to other drugs. Fassoulaki *et al.* reported that analgesia and opioid sparing with gabapentin was comparable to that of the sodium channel blocker, mexiletine.[74] Pandey *et al.* showed that both pain intensity and fentanyl consumption were significantly lower in patients receiving gabapentin before laparoscopic cholecystectomy, compared to those receiving tramadol.[76] Finally, we compared gabapentin to rofecoxib, and these two drugs combined, in patients undergoing hysterectomy.[83] Cumulative postoperative morphine consumption was similarly reduced in both single agent gabapentin and rofecoxib groups, with further significant reductions observed in the combination group. Pain evoked by cough was similar in both gabapentin and rofecoxib groups in this trial.

Secondary benefits

Given that early trials of gabapentin have demonstrated efficacy in the treatment of anxiety,[93,94] it is interesting to note that one perioperative trial showed an anxiolytic effect with gabapentin after knee surgery.[84]

TABLE III Perioperative randomized controlled trials of other anticonvulsant drugs

Ref.	*Drug*	*Control*	*n**	*Pain reduction*	*Opioid sparing*	*Adverse effects*
91	valproic acid	placebo ketoprofen	39	- (ketoprofen > placebo)	nr	nr
88	lamotrigine	placebo	30	+	nr	nr
90	pregabalin	placebo ibuprofen	30	+	nr	ns
89	oxcarbazepine	placebo	64	+	+	nr

*Approximately equally distributed across all study treatment groups; ns = not statistically significant; nr = not reported.

In light of previous suggestions that a reduction in movement-evoked pain correlates with improved postoperative function,[95] it is interesting to note that, in the setting of anterior cruciate ligament repair, preoperative gabapentin administration resulted in greater knee flexion angles on postoperative days one and two.[84] Furthermore, we have shown that postoperative pulmonary function, as assessed by peak expiratory flow rate, is improved with both gabapentin and rofecoxib.[83] The combination of these two drugs further enhances this response.[83] Taken together, these results suggest that gabapentin-induced reductions in movement-evoked pain may accelerate postoperative functional recovery. However, future studies with longer follow up are needed in order to determine whether these benefits translate into lower complication rates, earlier hospital discharge, or earlier return to work. Also, given the possibility that more aggressive pain management may prevent chronic post-surgical pain,[96] early evidence that perioperative treatment with gabapentin may reduce chronic post-surgical pain is particularly exciting.[74,82]

Other anticonvulsant medications

Few other trials have evaluated anticonvulsant medications for postoperative pain (Table III). In 1988, Martin *et al.* studied valproic acid, at a dose of 15 $mg \cdot kg^{-1}$, which showed no benefit over placebo, unlike the NSAID, ketoprofen, which was included as an active control.[91] Bonicalzi *et al.* reported substantial pain reductions with lamotrigine 200 mg for pain after transurethral prostate resection.[88] In 2001, Hill *et al.* published the first postoperative trial of an alpha-2-delta ligand which involved pregabalin.[90] After oral surgery, pregabalin 300 mg provided a significantly higher pain intensity difference than placebo.[90] The active comparator, ibuprofen 400 mg, showed a trend towards greater peak effect, whereas duration of action was longer with pregabalin. In preliminary abstract form, Sheen *et al.* recently reported on the analgesic and opioid sparing effects of oxcarbazepine after vaginal hysterectomy.[89]

Safety issues

Given the brief exposure and relatively small numbers of trial patients, it is apparent that the safety evaluation of anticonvulsant drugs administered in the perioperative setting is incomplete. Investigations of gabapentin for treatment of epilepsy and chronic pain suggest that this drug is associated with sedation and ataxia, as relatively common dose-dependent and reversible adverse effects.[97,98] Less commonly, weight gain and peripheral edema have been reported at gabapentin doses exceeding 1800 $mg \cdot day^{-1}$.[97,98] Clearly, more clinical investigation is required in order to better characterize the specific toxicities of gabapentin and other anticonvulsant drugs in the perioperative setting.

Conclusion

There are many available anticonvulsant drugs whose mechanisms of action may be important in treating post-surgical pain. Specific mechanisms include sodium and calcium channel antagonism, and decreased glutamate transmission. A growing body of preclinical evidence suggests that several anticonvulsant medications are antinociceptive in preclinical models of postoperative pain (e.g., carbamazepine, ethosuximide, gabapentin, lamotrigine, oxcarbazepine, pregabalin, and vigabitrin), and enhance opioid efficacy or suppress opioid analgesic tolerance. Results from recent clinical trials demonstrate analgesic efficacy, opioid sparing effect, and possible postoperative functional improvement associated with gabapentin. Other trials also suggest the potential analgesic efficacy of other anticonvulsant drugs including pregabalin, lamotrigine and possibly oxcarbazepine. Future research is needed to identify anticonvulsant drugs with the best perioperative therapeutic profile and, also, to further explore varying applications of these drugs (e.g., dose, timing, patient populations and co-administration

with other non-opioid analgesics) in order to optimize their clinical utility.

Acknowledgements

The author sincerely thanks Drs. Kenneth Kardash and Hance Clarke for their thoughtful comments made on previous versions of this manuscript.

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