The Effects of Gabapentin on Pre-Operative Anxiety, Morphine Consumption and Pain after Surgery.

by

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A thesis submitted in conformity with the requirements for the degree of Doctorate of Philosophy

Institute of Medical Sciences
University of Toronto

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Abstract

Gabapentin is an anticonvulsant that has become a treatment option for several indications that are not approved by Health Canada. Commonly, gabapentin is prescribed for neuropathic pain and anxiety disorders. The objective of this dissertation was to evaluate the efficacy of gabapentin for reducing pre-operative anxiety, post-operative pain and opioid consumption. The initial study examined regimens of pre-operative and post-operative gabapentin given to patients undergoing total knee arthroplasty. Patients that received gabapentin postoperatively used significantly less morphine at 24 hrs, 36 hrs and 48 hrs (p <0.05). Furthermore these patients had significantly better active-assisted knee flexion on postoperative day (POD) 2, POD 3, with a trend toward better flexion on POD 4. Next, we examined whether: 1) gabapentin administration reduces pain and opioid use after total hip arthroplasty using a multimodal analgesic regimen that included spinal anesthesia; and whether 2) preoperative administration of gabapentin is more effective than postoperative administration. Our results demonstrated that whether a 600 mg dose of gabapentin was given preoperatively or postoperatively, patients’ postoperative morphine consumption or pain scores were not reduced in hospital nor was there a reduction in pain 6 months after hip arthroplasty. The third study found that a single dose of 600 mg of gabapentin was not sufficient to reduce preoperative anxiety in patients prior to hip arthroplasty. In contrast,
the final study demonstrated that 1200 mg of gabapentin reduced pre-operative anxiety and pain catastrophizing in female patients with moderate to high levels of preoperative anxiety prior to major surgery, but also increased preoperative and early postoperative sedation. Our findings demonstrate the efficacy of perioperative gabapentin with respect to preoperative anxiety reduction and decreasing morphine consumption after surgery. Future studies that focus on the optimal dose and duration of perioperative gabapentin, with the aim of improving functional outcomes and decreasing the incidence and severity chronic post-surgical pain are warranted.
Acknowledgements

The pursuit of my PhD was not a task that I undertook lightly. It was an endeavour of perseverance, determination and I owe much gratitude to my family members, friends, professional colleagues and mentors who shared this path with me. Although challenging, and at times frustrating, it has truly been a rewarding experience and one that I would repeat again without hesitation.

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I am dedicating this dissertation to my two sons Quincy Hance Alexander Clarke and Noah Xavier Clarke. They are the joys of my life and I wish them much prosperity in their future endeavours. It is my hope that I have modeled for them the virtues of hard-work and perseverance in order to enable them to achieve their goals.
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<td>Analysis of variance</td>
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<tr>
<td>American Society of Anesthesiologists</td>
<td>ASA</td>
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<tr>
<td>Body Mass Index</td>
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<td>Cerebrospinal fluid</td>
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<td>Chronic Postsurgical Pain</td>
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<td>Numeric Rating Scale</td>
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<tr>
<td>Pain Catastrophizing Scale</td>
<td>PCS</td>
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<tr>
<td>Prostaglandin</td>
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<td>Per Os</td>
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<td>Post Anesthetic Care Unit</td>
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<td>Speilberger Trait Anxiety Index</td>
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<td>Three Times Daily</td>
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<tr>
<td>Total Hip arthroplasty</td>
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<td>Total knee arthroplasty</td>
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<td>Visual Analogue Scale</td>
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Chapter 1

Overview

The present dissertation, which examines the effects of gabapentin with respect to improving postoperative pain, reducing opioid consumption, and reducing preoperative anxiety in the perioperative period is divided into eight chapters. Chapter 1 presents a brief overview regarding the clinical evolution of gabapentin and presents information on the physiology and pharmacology of this medication. This chapter also explores documented and postulated mechanisms of action of gabapentin and explores the state of the literature when the studies started. Furthermore, I review the current literature with respect to the use of perioperative gabapentin and its effects on functional outcomes and the postulate that it reduces the incidence and severity of chronic post-surgical pain. Chapter 2 reviews the literature on postsurgical pain and provides information regarding the evolution from preemptive to preventive pain management in the perioperative time period. Multimodal analgesia is the mainstay of current perioperative pain practices and I review specific classes of medications that were used in the studies presented herein. Chapter 3 presents the objectives and hypotheses examined in the individual studies (i.e. chapters 4, 5, 6 and 7). Chapter 4 explores the effects of continuing gabapentin into the postoperative time period following total knee arthroplasty with respect to post-operative opioid consumption and active-assisted knee flexion. Chapter 5 is a randomized double blind controlled trial which was designed to determine whether; 1) a single 600 mg dose of gabapentin reduces pain and opioid use after Total Hip Arthroplasty (THA) using a multimodal analgesic regimen that included spinal anesthesia; and whether 2) preoperative administration of gabapentin is more effective than postoperative administration. Chapter 6 examines whether a single 600 mg preoperative dose
of gabapentin reduced preoperative anxiety in patients undergoing total hip arthroplasty. Chapter 7 further examines the efficacy of gabapentin to reduce preoperative anxiety. In Chapter 7, a population of women with moderate to high preoperative anxiety who are about to undergo major surgery is selected to receive 1200 mg of gabapentin 2 hours before surgery. The benefits of this dose of gabapentin in a highly anxious population was studied. Chapter 8 concludes this dissertation by providing a general discussion that summarizes the findings and presents the limitations of the studies. A brief exploration of the possible role for gabapentin and pregabalin for the prevention of chronic postsurgical pain will also be undertaken. Prior to concluding this dissertation, I will present my suggestions for future work.

1 Gabapentin

1.1 Clinical Evolution

Gabapentin, a structural analogue of γ-aminobutyric acid (GABA), was initially used as an anticonvulsant in the late 1980s (Figure 1.1).

Figure 1.1 Molecular Structures

(A) γ-aminobutyric acid  (B) Gabapentin  (C) Pregabalin (Chapter 8)
Clinically, gabapentin demonstrated poor efficacy as an anticonvulsant (Guay, 2003). However, the antinociceptive properties of this agent, along with the advantage of producing only mild adverse effects, made gabapentin an attractive therapeutic option for pain patients. The anticonvulsants that were being used for chronic pain patients had significant adverse effect profiles (i.e. carbamazepine) (Guay, 2003). In the late 1990s, a landmark paper found that gabapentin monotherapy produced the rapid onset of pain relief with relatively minor adverse effects in patients who suffered from chronic neuropathic pain induced by diabetes mellitus (Backonja, Beydoun, Edwards, Schwartz, Fonseca, Hes, LaMoreaux, & Garofalo, 1998). Currently, gabapentin is a first-line treatment for patients who suffer with chronic neuropathic pain (Laird & Gidal, 2000; Moulin, Clark, Gilron, Ware, Watson, Sessle, Coderre, Morley-Forster, Stinson, Boulanger, Peng, Finley, Taenzer, Squire, Dion, Cholkan, Gilani, Gordon, Henry, Jovey, Lynch, Mailis-Gagnon, Panju, Rollman, & Velly, 2007). In recent years, gabapentin has been used widely as an adjunct for the treatment of acute postsurgical pain. Gabapentin has been found to be effective in reducing postoperative pain following abdominal or pelvic surgery (Gilron, Orr, Tu, O'Neill, Zamora, & Bell, 2005b; Rorarius, Menander, Suominen, Rintala, Puura, Pirhonen, Salmelin, Haanpaa, Kujansuu, & Yli-Hankala, 2004; Turan, White, Karamanlioglu, Memis, Tasdogan, Pamukcu, & Yavuz, 2006b), musculoskeletal surgery (Clarke, Pereira, Kennedy, Gilron, Katz, Gollish, & Kay, 2009b; Pandey, Navkar, Giri, Raza, Behari, Singh, Singh, & Singh, 2005a; Turan, Karamanlioglu, Memis, Hamamcioglu, Tukenmez, Pamukcu, & Kurt, 2004a), head and neck surgery (Al-Mujadi, AR, Katzarov, Dehrab, Batra, & Al-Qattan, 2006; Mikkelsen, Hilsted, Andersen, Hjortso, Enggaard, Jorgensen, Hansen, Henriksen, & Dahl, 2006), breast surgery (Dirks, Fredensborg, Christensen, Fomsgaard, Flyger, & Dahl, 2002; A. Fassoulaki, K. Patris, C. Sarantopoulos, & Q. Hogan, 2002b; Fassoulaki, Triga, Melemeni, & Sarantopoulos,
2005b), varicocele surgery (Koc, Memis, & Sut, 2007) and thoracic surgery (Huot, Chouinard, Girard, Ruel, Lafontaine, & Ferraro, 2008).

Other studies have reported on the efficacy of gabapentin in the treatment of social anxiety disorder (Pande, Davidson, Jefferson, Janney, Katzelnick, Weisler, Greist, & Sutherland, 1999), bipolar disorder (Vieta, Manuel Goikolea, Martinez-Aran, Comes, Verger, Masramon, Sanchez-Moreno, & Colom, 2006), panic disorder (Pande, Pollack, Crockatt, Greiner, Chouinard, Lydiard, Taylor, Dager, & Shiovitz, 2000), obsessive compulsive disorder (Onder, Tural, & Gokbakan, 2008), and post-traumatic stress disorder (Brannon, Labbate, & Huber, 2000; Hamner, Brodrick, & Labbate, 2001; Stein, Kerridge, Dimsdale, & Hoyt, 2007). One unique trial examined the anxiolytic potential of gabapentin for anxiety induced by public speaking and found that other than a decrease in hostility in the pre and post-stress states there was no difference in physiological parameters (i.e. heart rate and blood pressure) nor in anxiety (de-Paris, Sant'Anna, Vianna, Barichello, Busnello, Kapczinski, Quevedo, & Izquierdo, 2003).

The treatment of preoperative anxiety with gabapentin has become an area of recent interest, with published studies showing mixed results (Clarke, Kay, Orser, Gollish, Mitsakakis, & Katz, 2010; Menigaux, Adam, Guignard, Sessler, & Chauvin, 2005; Tirault, Foucan, Debaene, Frasca, Lebrun, Bernard, Sandefo, & Van Elstraete, 2010). In the perioperative period, gabapentin causes mild adverse events such as somnolence (20%), dizziness (18%), ataxia (13%) and fatigue (11%) (Rose & Kam, 2002). Finally, several meta-analyses have confirmed the efficacy of gabapentin in reducing postoperative opioid use and pain scores (Ho, Gan, & Habib, 2006b; Peng, Wijeysundera, & Li, 2007; Seib & Paul, 2006).
Recent basic science research has demonstrated that gabapentin increases tonic inhibitory currents in murine hippocampal neurons. (Cheng, Bonin, Chiu, Newell, MacDonald, & Orser, 2006) Work is ongoing with respect to elucidating the possible central role of the gabapentinoinds in the mammalian central nervous system. It is likely that there are both peripheral and central mechanisms that mediate the clinical effects of these medications.

1.2 Physiology and Pharmacology

The L-amino acid transport system, which is expressed in the intestine, the blood-brain barrier and the nervous system, is responsible for the absorption of gabapentin and pregabalin (Su, Feng, & Weber, 2005; Su, Lunney, Campbell, & Oxender, 1995). Absorption kinetics of gabapentin are dose dependent, due to the saturable L-amino transport system. The bioavailability of a single 300 mg oral dose of gabapentin is approximately 50% and decreases with increasing dose. Gabapentin is not metabolized in humans and is eliminated from the body through renal clearance. The elimination half-life of gabapentin is approximately 5 to 7 hours (Beydoun, Uthman, & Sackellares, 1995). There are no known drug-drug interactions, but antacids reduce the bioavailability of gabapentin by approximately 20%, and proton pump inhibitors decreases the clearance of gabapentin by approximately 12% (Cheng & Chiou, 2006; Rose & Kam, 2002).

1.3 Antinociceptive Mechanism of Action

The proposed antinociceptive properties of gabapentin is believed to result from the selective binding to the $\alpha_2\delta$ subunit of voltage-dependent calcium channels in activated neurons (Cheng & Chiou, 2006). There is a specific high-affinity drug binding site localized to synapses (Taylor, 2009). The binding of the drug to the $\alpha_2\delta$ subunit of voltage-dependent
calcium channels in excited neurons at synapses is both necessary and sufficient to account for the analgesic drug actions which are apparently caused by the decreased release of neurotransmitters (Taylor, 2009).

Gabapentin, a structural analogue of γ-aminobutyric acid, has been used as an anticonvulsant and antinociceptive drug. Its main binding site is the α2δ subunit of voltage-dependent calcium channels (Cheng & Chiou, 2006). Gabapentin is effective for neuropathic pain, diabetic neuropathy, postherpetic neuralgia, and reflex sympathetic dystrophy (Backonja, Beydoun, Edwards, Schwartz, Fonseca, Hes, LaMoreaux, & Garofalo, 1998). Gabapentin has antihyperalgesic actions that selectively affect central sensitization (Rose & Kam, 2002). Many clinical trials have examined the efficacy of gabapentin for the treatment of early postsurgical pain. The surgical populations studied include abdominal or pelvic surgery (Dierking, Duedahl, Rasmussen, Fomsgaard, Moiniche, Romsing, & Dahl, 2004; Fassoulaki, Stamatakis, Petropoulos, Siafaka, Hassiakos, & Sarantopoulos, 2006b; Gilron, et al., 2005b; Pandey, Priye, Singh, Singh, Singh, & Singh, 2004a; Pandey, Singhal, Kumar, Lakra, Ranjan, Pal, Raza, Singh, & Singh, 2005b; Ronarius, et al., 2004; Turan, Karamanlioglu, Memis, Usar, Pamukcu, & Ture, 2004b; Turan, et al., 2006b), musculoskeletal surgery (Adam, Menigaux, Sessler, & Chauvin, 2006; Leung, Sands, Rico, Petersen, Rowbotham, Dahl, Ames, Chou, & Weinstein, 2006; Menigaux, et al., 2005; Pandey, et al., 2005a; Pandey, Sahay, Gupta, Ambesh, Singh, Raza, Singh, & Singh, 2004b; Radhakrishnan, Bithal, & Chaturvedi, 2005; Turan, et al., 2004a; Turan, Kaya, Karamanlioglu, Pamukcu, & Apfel, 2006a), head and neck surgery (Al-Mujadi, et al., 2006; Mikkelsen, et al., 2006; Turan, Memis, Karamanlioglu, Yagiz, Pamukcu, & Yavuz, 2004c), breast surgery (Dirks, et al., 2002; A. Fassoulaki, et al., 2002b; Fassoulaki, et al., 2005b; Parsa, Sprouse-Blum, Jackowe,
Lee, Oyama, & Parsa, 2008), varicocele surgery (Koc, et al., 2007) and thoracic surgery (Huot, et al., 2008). Most of these randomized, controlled trials, studied a single dose of gabapentin given prior to surgery. Only 4 of the trials mentioned above failed to demonstrate a decrease in pain scores or an opioid sparing effect in the early postsurgical period (Adam, et al., 2006; Fassoulaki, et al., 2006b; Leung, et al., 2006; Radhakrishnan, et al., 2005).

### 1.4 Other Postulated Mechanisms

Evidence by Bonin and colleagues demonstrates that gabapentin may interact with other molecular targets other than the α2δ calcium channels within the central nervous system (CNS) (Bonin, Labrakakis, Eng, Whissell, Koninck, & Orser, 2011). Gabapentin was initially developed to mimic the actions of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). A cyclohexane ring was added to the carbon backbone of GABA to facilitate the transfer of the drug across the blood-brain barrier (Goa & Sorkin, 1993). Interestingly, gabapentin does not bind to, or directly modulate, GABA<sub>A</sub> receptors (Cheng, et al., 2006; Macdonald & Greenfield, 1997; Rock, Kelly, & Macdonald, 1993) nor does it modulate GABA<sub>B</sub> receptors except at high concentrations (Sills, 2006).

The auxiliary α2δ subunit of voltage-dependent calcium channels is a high affinity binding site of gabapentin and pregabalin in the central nervous system (Gee, Brown, Dissanayake, Offord, Thurlow, & Woodruff, 1996; Suman-Chauhan, Webdale, Hill, & Woodruff, 1993). The α2δ subunit binds to, and increases the expression and conductance of, voltage-dependent calcium channels (Felix, Gurnett, De Waard, & Campbell, 1997). The α2δ subunit is widely expressed in many tissues and is highly expressed in the CNS (Cole, Lechner, Williams, Prodanovich, Bleicher, Varney, & Gu, 2005). Notably, the expression of the α2δ subunit in the spinal cord dorsal horn is up-regulated in an animal model of allodynic pain
(Li, Song, Higuera, & Luo, 2004), while the over expression of the $\alpha_2\delta$ subunit in mice produces tactile allodynia and thermal hyperalgesia (Li, Zhang, Matthews, Li, Kurwa, Boroujerdi, Gross, Gold, Dickenson, Feng, & Luo, 2006).

Several lines of evidence suggest that the high-affinity binding to the $\alpha_2\delta$ subunit of voltage-dependent calcium channels contributes to, but may not fully account for, the analgesic properties of gabapentin. The increased expression of the $\alpha_2\delta$ subunit that occurs in animal models of hyperalgesia is not a prerequisite for the short-term analgesic actions of gabapentin (Luo, Chaplan, Higuera, Sorkin, Stauderman, Williams, & Yaksh, 2001). In addition, a comparison of the antinociceptive properties of gabapentin and stereoisomeric analogues of gabapentin revealed a stereospecific analgesic effect of these gabapentin analogues in acute or persistent pain (Urban, Ren, Park, Campbell, Anker, Stearns, Aiyar, Belley, Cohen, & Bristow, 2005). However, some of the gabapentin analogues with affinity for the $\alpha_2\delta$ did not have antinociceptive properties.

Recent evidence suggests that the $\alpha_2\delta$ subunit also regulates synaptogenesis through mechanisms that are independent of Ca$^{2+}$ channel function (Eroglu, Allen, Susman, O'Rourke, Park, Ozkan, Chakraborty, Mulinyawe, Annis, Huberman, Green, Lawler, Dolmetsch, Garcia, Smith, Luo, Rosenthal, Mosher, & Barres, 2009). Specifically, the $\alpha_2\delta$ subunit is a receptor for thrombospondins – proteins that are secreted by astrocytes that promote synapse formation (Christopherson, Ullian, Stokes, Mullowney, Hell, Agah, Lawler, Mosher, Bornstein, & Barres, 2005). Gabapentin disrupts the interaction between thrombospondins and the $\alpha_2\delta$ subunit, resulting in decreased synapse formation (Eroglu, et al., 2009). The disruption of $\alpha_2\delta$ subunit-mediated synaptogenesis by gabapentin may also contribute to the analgesic effects of gabapentin for the treatment of chronic pain.
Based on the above evidence, gabapentin has been proposed to act through a wide variety of mechanisms beyond inhibiting the actions of the α2δ subunit protein. Gabapentin has been shown to inhibit glutamate release (Errante & Petroff, 2003), increase the activity of NMDA receptors (Cheng, et al., 2006), inhibit the activity of voltage-gated sodium channels (Pan, Eisenach, & Chen, 1999; Wamil & McLean, 1994), and enhance the activity of voltage-gated potassium channels (Sills, 2006). Additionally, prolonged exposure to gabapentin can increase the amplitude of a tonic inhibitory GABAergic conductance (Cheng, et al., 2006) that may also regulate pain processes (Bonin, et al., 2011).

1.5 Pre-operative Anxiety

Recent studies have found that the lifetime prevalence of anxiety may be as high as 18%, which would make anxiety the most prevalent of all mental disorders (Kessler, Demler, Frank, Olfson, Pincus, Walters, Wang, Wells, & Zaslavsky, 2005). The largest randomized controlled trial to date (n = 420 patients) investigated gabapentin treatment of anxiety following breast cancer survival (Lavigne, Heckler, Mathews, Palesh, Kirshner, Lord, Jacobs, Amos, Morrow, & Mustian, 2012). Lavigne and colleagues measured anxiety using the Speilberger Strait-Trait Anxiety Inventory at baseline, 4 and 8 weeks. Improvement in anxiety symptoms from baseline favored gabapentin at 4 and 8 weeks.

The most common emotions experienced by patients scheduled for major surgery are fear and anxiety. Fear and anxiety are distinct emotions even though they have a good deal in common. The situations and factors that produce them and the subjective states associated with these emotions are often the same. However, one of the main differences between them involves the temporal relation to the presentation of the perceived threat. Fear is defined as
the emotional response to a present or ongoing threat, while anxiety is the response to potential or future threat. (Blanchard & Blanchard, 2008) Given this distinction, the actions that accompany fear and anxiety will also differ with escape and avoidance behaviours associated with the former and latter, respectively.

Patient about to undergo surgery, and those in the days after surgery, are fearful and anxious about many things; including, the hospital environment, being away from home, invasive medical procedures, diagnostic uncertainty, and post-surgical pain. Pain is influenced by a host of factors, such as culture, the meaning of the situation, attention-diversion and distraction, feelings of control, suggestion and placebos, and fear and anxiety. (Katz & Melzack, 2009) Preoperative anxiety and fear-based states have been shown to be associated with (1) the intensity of acute postoperative pain and analgesic consumption (Katz, Buis, & Cohen, 2008b), as well as (2) the development of chronic postsurgical pain (CPSP) (Forsythe, Dunbar, Hennigar, Sullivan, & Gross, 2008; Harden, Bruehl, Stanos, Brander, Chung, Saltz, Adams, & Stulberg, 2003; Sullivan, Tanzer, Stanish, Fallaha, Keefe, Simmonds, & Dunbar, 2009). Other studies have shown that psychosocial factors, measured post-hospital discharge, are predictive of subsequent CPSP and pain disability (Katz, Asmundson, McRae, & Halket, 2008a).

The efficacy of benzodiazepines for the treatment of pre-operative anxiolysis in adults and children has been well documented (Giacalone, 1992; Wright, Stewart, Finley, & Buffett-Jerrott, 2007). Novel anti-anxiety techniques/agents continue to be investigated for the pediatric population (Almenrader, Passariello, Coccetti, Haiberger, & Pietropaoli, 2007; Golan, Tighe, Dobija, Perel, & Keidan, 2009). Until recently, there have been very few studies that examined alternative pharmacological interventions for the treatment of
preoperative adult anxiety. Gabapentin is used “off-label” for the treatment of preoperative anxiety.

Recent studies suggest that gabapentin and pregabalin, which are $\alpha_2\delta$ voltage-dependent calcium channel modulators, may be effective for preoperative anxiolysis. However, these studies produced mixed results (Clarke, et al., 2010; Menigaux, et al., 2005; Tirault, et al., 2010). Patients who received gabapentin 1200 mg prior to surgery to repair the anterior cruciate ligament reported less preoperative anxiety on the operating table prior to induction of anesthesia compared to placebo-treated controls (Menigaux, et al., 2005). In other studies, gabapentin 1200 mg did not reduce preoperative anxiety when compared to the benzodiazepine, oxazepam (15 mg) in patients undergoing vaginal hysterectomy (Rorarius, et al., 2004), nor did gabapentin 600 mg provide anxiolysis prior to total hip arthroplasty when administered 2 hours prior to the induction of anesthesia (Clarke, et al., 2010). Two of these studies did not include pre-drug baseline anxiety scores (Menigaux, et al., 2005; Rorarius et al., 2004). Also, one failed to include an appropriate placebo-control condition (Rorarius, et al., 2004) and another recruited patients with low levels of preoperative anxiety (Clarke, et al., 2010). Chapters 6 and 7 of this dissertation examine the efficacy of gabapentin in the treatment of anxiolysis.

1.6 State of The Acute Postoperative Pain Literature Upon Initiation of Dissertation

Prior to commencing our research 6 years ago, there had been 20 studies examining the effect of gabapentin on postoperative pain (Al-Mujadi, et al., 2006; Dierking, et al., 2004; Dirks, et al., 2002; A. Fassoulaki, et al., 2002b; Fassoulaki, et al., 2006b; Fassoulaki, et al., 2005b; Gilron, et al., 2005b; Menigaux, et al., 2005; Mikkelsen, et al., 2006; Pandey, et al., 2005a;
Pandey, et al., 2004a; Pandey, et al., 2004b; Radhakrishnan, et al., 2005; Rorarius, et al., 2004; Turan, et al., 2004a; Turan, et al., 2004b; Turan, et al., 2006b). All but one of these studies (Radhakrishnan, et al., 2005) found that gabapentin significantly reduced the amount of postoperative opioid required (16-67%) and a simultaneous reduction in pain scores. There was no difference in side effect profile between the gabapentin and the control groups in 11 studies (Al-Mujadi, et al., 2006; Dierking, et al., 2004; Dirks, et al., 2002; Fassoulaki, Melemeni, Paraskeva, & Petropoulos, 2006a; Fassoulaki, et al., 2005b; Menigaux, et al., 2005; Pandey, et al., 2004a; Pandey, et al., 2005b; Radhakrishnan, et al., 2005; Turan, et al., 2004a; Turan, et al., 2006a), while one (Turan, et al., 2004a) found a higher incidence of nausea and urinary retention in the control groups, and two studies (Mikkelsen, et al., 2006; Pandey, et al., 2004a) found a higher incidence of nausea/vomiting in the gabapentin group. The most common side effect was increased sedation which was found in only 4 studies when doses greater than 900 mg per day were given (Gilron, et al., 2005b; Mikkelsen, et al., 2006; Pandey, et al., 2005a; Pandey, et al., 2004a).

The optimal preoperative dose of gabapentin had been suggested by Pandey and colleagues, who published a dose-response study of 100 patients that evaluated the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar discectomy (Pandey, et al., 2005a). In this study, different doses of preoperative gabapentin, 300 mg, 600 mg, 900 mg and 1200 mg, were compared to placebo. In accordance with previous studies, this group demonstrated that the preoperative use of gabapentin (300–1200 mg) significantly reduced the severity of pain in patients after single-level lumbar discectomy. Postoperatively, these patients had significantly lower pain scores at time points 6, 12, 18, and 24 hours and had significantly decreased opioid consumption in the initial 24 hours in comparison to the patients who received placebo. More specifically, patients who received gabapentin 600 mg,
900 mg, and 1200 mg had lower Visual Analogue Pain Scores (VAS) at all time points compared to patients who received gabapentin 300 mg. Increasing the dose of gabapentin from 600 to 1200 mg did not decrease the VAS score, nor did the increasing dose of gabapentin significantly decrease fentanyl consumption. Thus, Pandey and colleagues concluded that gabapentin 600 mg is the optimal preoperative dose for postoperative pain relief following lumbar discectomy (Pandey, et al., 2005a). This study was the first to systematically examine a preoperative dose response curve for gabapentin in terms of VAS pain scores, opioid consumption and side effects in the immediate postoperative period. Based on the above study, we chose to administer gabapentin 600 mg preoperatively to our patients. Other studies have also used lower doses of preemptive gabapentin and have demonstrated decreased opioid consumption and decreased postoperative pain scores (Pandey, et al., 2004a; Pandey, et al., 2004b).

There had been 8 studies that probed the administration of gabapentin in the postoperative period (Dierking, et al., 2004; A. Fassoulaki, K. Patris, C. Sarantopoulos, & Q. Hogan, 2002a; Fassoulaki, et al., 2006b; Fassoulaki, et al., 2005b; Gilron, 2006; Mikkelsen, et al., 2006; Turan, et al., 2006a; Turan, et al., 2006b). Fassoulaki and colleagues (A. Fassoulaki, et al., 2002a) examined postoperative pain scores and opioid consumption in breast cancer patients who underwent surgery. Seventy-five patients undergoing surgery for breast cancer were randomized to receive mexiletine 600 mg/day, gabapentin 1200 mg/day or placebo for 10 days. Opioid consumption was reduced by 50% in the gabapentin and mexiletine groups vs. the placebo group on days 2-10. Only the gabapentin group showed decreased pain after movement from the 2nd to the 5th postoperative day. There were no adverse effects reported in the gabapentin group. Dierking (2004) and his colleagues randomized 80 patients to receive gabapentin (1200 mg) or placebo 1 hr preoperatively, then either gabapentin 600 mg or
placebo at hours 8, 16, and 24 postoperatively following abdominal hysterectomies (Dierking, et al., 2004). Opioid consumption was reduced by 32% and there was no significant difference between side effects between either group. Another study that examined the effects of gabapentin outcomes was published by Gilron and his colleagues who randomized 110 patients to 4 study groups: (A) placebo (B) gabapentin 600 mg TID (C) rofecoxib 50 mg/day (D) gabapentin 600 mg TID plus rofecoxib 50 mg/day. Drugs were administered starting 1hr preoperatively and were continued for 72 hours postoperatively (Gilron, et al., 2005b). This study was unique because it went further than simply looking at pain scores and morphine consumption data. Gilron and his colleagues demonstrated that the gabapentin and the gabapentin plus rofecoxib groups experienced significantly less movement-associated pain evoked by sitting and coughing after abdominal hysterectomy. Adverse events were similar in all groups except for the level of sedation, which was more frequent in the gabapentin treated groups. Consistent with previous literature, the multimodal gabapentin/rofecoxib combination demonstrated opioid sparing, lower pain scores, but most importantly, decreased movement-associated pain. This is important because decreasing movement-associated pain could be a significant factor in faster rehabilitation. Only four studies had prescribed gabapentin beyond 72 hours postoperatively (A. Fassoulaki, et al., 2002a; Fassoulaki, et al., 2006b; Fassoulaki, et al., 2005b; Mikkelsen, et al., 2006). This is an area in which further research is needed to determine whether prolonged postoperative administration and its benefits translate into earlier hospital discharge, decreased chronic pain rates and increased functional recovery even beyond the acute postsurgical time period. Chapters 4 and 5 examines some of these issues.

The literature to date supported the effectiveness of gabapentin in reducing postoperative pain and opioid consumption. A meta-analysis (Seib & Paul, 2006) and a systematic review (Ho,
Gan, & Habib, 2006a) reported that gabapentin has an opioid sparing effect and reduces pain scores in the acute postoperative period. However, even though the above literature exists, the use of gabapentin in the perioperative period is not as prevalent as one might expect. For example, of the teaching hospitals in the Toronto area, at that time, Sunnybrook Health Sciences Centre was the only centre using gabapentin routinely for almost all patients that undergo elective total knee arthroplasty and total hip arthroplasty procedures. Our group intended to test the novel hypothesis that the rate and extent of rehabilitation would be greater in patients who receive perioperative gabapentin than placebo treated controls. Our proposed study (Chapter 5) will follow patients up to 6 months post surgery.

1.7 Current literature: Does Gabapentin Prevent Chronic Postsurgical Pain?

Over 50 randomized controlled trials have been published which examined gabapentin as an adjunct for the treatment of acute postsurgical pain. The evidence supports that gabapentin decreases opioid consumption and reduces acute postoperative pain (Tiippana, Hamunen, Kontinen, & Kalso, 2007). Recently studies have been published which postulate that gabapentin may also be a useful agent in the reduction of the incidence and intensity of chronic postsurgical pain (Amr & Yousef, 2010; Brogly, Wattier, Andrieu, Peres, Robin, Kipnis, Arnalsteen, Thielemans, Carnaille, Pattou, Vallet, & Lebuffe, 2008; Clarke, Pereira, Kennedy, Andrion, Mitsakakis, Gollish, Katz, & Kay, 2009a; A. Fassoulaki, et al., 2002b; Fassoulaki, et al., 2005b; Moore, Costello, Wieczorek, Shah, Taddio, & Carvalho, 2011; Sen, Sizlan, Yanarates, Emirkadi, Ozkan, Dagli, & Turan, 2009a; Sen, Sizlan, Yanarates, Senol, Inangil, Sucullu, Ozkan, & Dagli, 2009b).
One might be skeptical about the possibility of uncovering pain and functional outcome differences between gabapentin treated patients and controls that last 3 to 6 months after surgery. However, Fassoulaki and colleagues demonstrated in two studies that the incidence of chronic pain can be significantly reduced by perioperative treatment with gabapentin (Fassoulaki, et al., 2006b; Fassoulaki, et al., 2005b). Furthermore, Fassoulaki (2005) and colleagues demonstrated that the incidence of chronic pain was reduced in patients who underwent breast surgery were given gabapentin for 8 days and local anesthetics were injected into the surgical site at the time of closure (Fassoulaki, et al., 2005b). The decreased incidence of chronic pain was demonstrated at 3 months (57% gabapentin vs. 82% placebo) and remained significant at 6 months (30% gabapentin vs. 45% placebo) post breast surgery. The above findings support our hypothesis that functional outcome gains made by patients in the acute postoperative period may translate into long-term effects, and supports the presumption that multimodal treatments are necessary to prevent chronic pain. Patients treated with gabapentin in the acute perioperative period have decreased pain at rest and with movement (A. Fassoulaki, et al., 2002b; Fassoulaki, et al., 2006b; Gilron, et al., 2005b; Menigaux, et al., 2005) This improved pain control may translate into a head start with rehabilitation in comparison to patients who do not receive the medications.

CPSP has been defined as pathological pain that persists for longer than two months after surgery (Macrae & Davies, 1999). The factors that influence the transition from acute postoperative pain to chronic postsurgical pain (CPSP) have yet to be elucidated. Several patient-related and surgical factors have been linked to the development of CPSP (Katz & Seltzer, 2009). The most consistent patient factor is the presence and/or intensity of preoperative and postoperative pain (Katz, 1997; Kehlet, Jensen, & Woolf, 2006; Perkins & Kehlet, 2000). Because moderate to severe postoperative pain is a frequent occurrence after
surgery (Apfelbaum, Chen, Mehta, & Gan, 2003), novel pharmacological agents such as gabapentin, in addition to traditional opioids, are administered with the aim of providing superior pain relief at rest and with movement; reducing opioid consumption and reducing analgesic-related adverse effects (Adam, et al., 2006; Gilron, et al., 2005b; Menigaux, et al., 2005). If pharmacological agents, such as gabapentin can prevent the establishment of surgery-induced central sensitization and can decrease postoperative pain (Mathiesen, Jacobsen, Holm, Randall, Adamiec-Malmstroem, Graungaard, Holst, Hilsted, & Dahl, 2008; McCartney, Sinha, & Katz, 2004; Pandey, et al., 2004a), then these drugs, given during the perioperative period, may also play a role in preventing the transition of acute pain to chronic pain.

Neuropathic pain, which is defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system (Loeser & Treede, 2008), has been implicated as a major contributor to the development of CPSP (Costigan, Scholz, & Woolf, 2009; Katz & Seltzer, 2009). Given that gabapentin is a front-line treatment for patients suffering from established chronic neuropathic pain (Gilron, Bailey, Tu, Holden, Jackson, & Houlden, 2009; Ifuku, Iseki, Hidaka, Morita, Komatus, & Inada, 2011), it is plausible that this medication, when used in the perioperative setting, may be of benefit in reducing the incidence and/or intensity of chronic postsurgical pain.

Eight trials (up to end of 2011) reported outcomes on the incidence of chronic postsurgical pain following the administration of gabapentin in the acute perioperative period. Of the eight gabapentin trials, four (Brogly, et al., 2008; Fassoulaki, Triga, Melemeni, & Sarantopoulos, 2005a; Sen, et al., 2009a; Sen, et al., 2009b) reported that the perioperative use of gabapentin resulted in a lower incidence of pain and/or lower analgesic requirements at
long-term follow-up (≥ two months after surgery). Table 1.1 summarizes the results.

**Table 1.1 Gabapentin Studies Reporting Pain Outcomes 2 months or longer after surgery**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study</th>
<th>Postoperative outcome results</th>
</tr>
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<tbody>
<tr>
<td>Chronic postsurgical pain</td>
<td>Amr et al (2010)</td>
<td>Venlafaxine demonstrated a greater preventive effect with respect to decreasing chronic pain vs. placebo-treated patients (i.e. less burning and stabbing/pricking pain) at 6 months. Patients who received gabapentin reported less burning than control patients</td>
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<tr>
<td></td>
<td>Brogley et al (2008)</td>
<td>Significantly more patients in the placebo group (7/24 – 30%) fit the DN2 criterion for chronic neuropathic pain than did the patients who received gabapentin after thyroid surgery with SCPB (1/23 – 4.3%) 6 months after surgery</td>
</tr>
<tr>
<td></td>
<td>Clarke et al (2009)</td>
<td>Six months following total hip athroplasty surgery, the incidence and severity of chronic postsurgical pain was similar in all groups</td>
</tr>
<tr>
<td></td>
<td>Fassoulaki et al (2002)</td>
<td>Three months after surgery, the incidence of chronic pain, its severity and the need for supplemental analgesics were not affected by either intervention. There was a report of increased “burning” pain in the control group vs. the other two groups</td>
</tr>
<tr>
<td></td>
<td>Fassoulaki et al (2005)</td>
<td>3 and 6 months after surgery, 18 of 22 (82%) and 12 of 21 (57%) of the controls reported chronic pain versus 10 of 22 (45%) and 6 of 20 (30%) in the treatment group. A significant difference was evident at 3 months, but not 6 months</td>
</tr>
<tr>
<td></td>
<td>Moore et al (2011)</td>
<td>Three months after surgery, the incidence of chronic pain, its severity and the need for supplemental analgesics were similar between groups</td>
</tr>
<tr>
<td></td>
<td>Sen et al (2009)</td>
<td>The severity of incisional pain was significantly less in the gabapentin-treated group at 1, 3 and 6 months</td>
</tr>
<tr>
<td></td>
<td>Sen et al (2009)</td>
<td>The severity of incisional pain was significantly less in the gabapentin-treated group at 1, 3 and 6 months</td>
</tr>
</tbody>
</table>

**Legend:** SCPB = Superficial cervical plexus block; vs = Versus
Brogly et al. (Brogly, et al., 2008) administered 1200 mg of gabapentin (n=25) or placebo (n=25) two hours before total thyroidectomy surgery. Patients also received superficial cervical plexus blocks; a significant difference in opioid consumption or pain scores were not observed during the first 24 hours after surgery (Brogly, et al., 2008). Using the neuropathic pain diagnostic questionnaire (DN2) as a diagnostic tool, Brogly et al. (Brogly, et al., 2008) found that 30% (7 of 24) of patients reported neuropathic pain in the placebo group compared with 4% (1 of 23) of gabapentin-treated patients at six months after surgery.

Using a similar design (i.e. 1200 mg gabapentin (n=30) 1 hour prior to inguinal herniorrhaphy with spinal anesthesia, Sen et al. (Sen, et al., 2009b) reported that patients who received gabapentin had less intense pain at one, three and six months after surgery. The gabapentin-treated patients reported less interruption with their activities of daily living 1 month postsurgery (Sen, et al., 2009b).

In another study by Sen et al (Sen, et al., 2009a) 40 women were randomly assigned to receive placebo (n=20) vs. intraoperative ketamine until the end of surgery (n=20) vs. 1200 mg gabapentin 1 hour before total abdominal hysterectomy. Patients who received gabapentin had lower pain scores and consumed less opioids in the acute postoperative period (24 hours). The incidence of incisional pain and pain intensity at one, three and six months after surgery were significantly lower in the gabapentin group compared with the ketamine and control groups (Sen, et al., 2009a).

As mentioned earlier, Fassoulaki and colleagues (Fassoulaki, et al., 2005a) found a reduction in pain and analgesic consumption using a multimodal analgesic regimen. This study involved 50 women who underwent breast cancer surgery that were randomly assigned to receive 1200 mg gabapentin (for eight postoperative days) starting the evening before
surgery, a eutectic mixture of local anesthetic cream (for three postoperative days) and ropivacaine in the wound (at wound closure) (n=25) and were compared with placebo (n=25) (Fassoulaki, et al., 2005a). The group that received the multimodal analgesic regimen used significantly less paracetamol and adjunctive pain medications than controls; they also reported lower pain scores at rest and with movement on postoperative days 1, 2, 4 and 8. At three months after surgery, the patients who were in the multimodal analgesia group reported a significantly lower incidence of chronic pain (82% vs. 45%) and used fewer supplemental analgesics (23% vs. 0%) than patients that received only placebo. Six months after surgery, 57% of control patients complained of chronic pain compared with 30% in the treatment group; however, this was not a statistically significant finding.

The remaining four studies reported no effect of gabapentin on pain or supplemental analgesic use more than two months after surgery (Amr & Yousef, 2010; Clarke, et al., 2009a; A. Fassoulaki, et al., 2002b; Moore, et al., 2011). A closer examination of two of the negative gabapentin studies (Amr & Yousef, 2010; Argyro Fassoulaki, Konstantinos Patris, Costantine Sarantopoulos, & Quinn Hogan, 2002) showed that although there was no difference in the incidence or severity of CPSP after breast cancer surgery at the three-month and six-month follow-up, both studies found that patients who received gabapentin reported less burning pain at these time points.

### 1.8 Gabapentin and Functional Outcomes

Three studies have attempted to measure the impact of perioperative gabapentin on daily function in the long term. The three gabapentin trials assessed this outcome by asking the patients: “What impact does pain currently have on your daily activities?” (Moore, et al., 2011; Sen, et al., 2009a; Sen, et al., 2009b) Two gabapentin trials reported that a single 1200
mg dose of gabapentin was associated with improved daily functioning one month after inguinal herniorrhaphy (Sen, et al., 2009b) and one and three months after total hysterectomy (Sen, et al., 2009a). However a study by Moore reported that a single 600 mg dose of gabapentin did not affect functional outcomes or disability three months following caesarian section surgery (Moore, et al., 2011).

Osteoarthritis (OA), the most common reason for total hip and knee arthroplasty, accounts for more difficulty with climbing stairs and walking than any other disease (Felson, Lawrence, Dieppe, Hirsch, Helmick, Jordan, Kington, Lane, Nevitt, Zhang, Sowers, McAlindon, Spector, Poole, Yanovski, Ateshian, Sharma, Buckwalter, Brandt, & Fries, 2000; Guccione, Felson, Anderson, Anthony, Zhang, Wilson, Kelly-Hayes, Wolf, Kreger, & Kannel, 1994). Since one of the primary goals of total knee arthroplasty is to improve physical function, this provides an ideal model to study the effects of gabapentin on functional outcomes. While many trials have demonstrated reduced movement-induced postsurgical pain, (Al-Mujadi, et al., 2006; Dirks, et al., 2002; Fassoulaki, et al., 2005b; Gilron, et al., 2005b; Menigaux, et al., 2005; Rorarius, et al., 2004; Turan, et al., 2006b), whether this translates into accelerated recovery and/or improved functional outcomes remains unknown. Future trials must evaluate the effects of gabapentin on recovery following total joint arthroplasty, within the context of multimodal analgesia. Outcomes for such trials should include both self-report and performance-based measures of physical function, (Stratford & Kennedy, 2006; Stratford, Kennedy, & Woodhouse, 2006) such as the 6-minute walk test (Boardman, Dorey, Thomas, & Lieberman, 2000; Kreibich, Vaz, Bourne, Rorabeck, Kim, Hardie, Kramer, & Kirkley, 1996), the timed up and go test (Freter & Fruchter, 2000; Ouellet & Moffet, 2002) and a timed stair test (Kennedy, Stratford, Pagura, Walsh, & Woodhouse, 2002; Walsh, Kennedy, Stratford, & Woodhouse, 2001; Walsh, Woodhouse, Thomas, & Finch, 1998), all of which
demonstrated reliability and sensitivity to change within the total joint arthroplasty population (Kennedy, Stratford, Wessel, Gollish, & Penney, 2005).
Chapter 2

2. Literature Review

2.1 Physiology of Postsurgical Pain

The classic pain pathway was once described as a neuronal signaling pathway that commenced in the periphery following an injury or a noxious event and was then transduced via nociceptive receptors (nociceptors) and transmitted along the primary afferents to the spinal cord then upwards to the brain (Melzack & Wall, 1988). Nociceptive sensory neurons transduced physical noxious energy into an electrical signal. The electrical signal (i.e. action potentials) transmitted the location and the intensity of the noxious stimulus via the spinal cord to the brain (Woolf & Salter, 2000). This classic view of pain sensation lacked the integration of the role of the cerebral cortex with respect to pain perception and control (Melzack & Katz, 2007).

After surgical incision, inflammatory mediators released by damaged tissue trigger an inflammatory cascade. This inflammatory response reduces the threshold and increases the responsiveness of nociceptors (sensory receptors on C-fibers and Aδ fibres) to subsequent input in the damaged tissue; a phenomenon known as peripheral sensitization (Costigan, et al., 2009; Fitzgerald, 2005). The body’s neurophysiological responses to any insult, including surgery, may initially serve a protective function (i.e. pain limits further use) and promote healing. It is now known that similar sensitization processes can also occur more centrally as a result of the “afferent barrage” induced by activation of nociceptors in response to surgery. Central sensitization refers to an alteration in the response properties of central neurons (e.g., in the dorsal horn of the spinal cord). Features of central sensitization include an increased responsiveness to activation, reduced threshold, expanded receptive fields, and spontaneous
activity following injury (Latremoliere & Woolf, 2009; Woolf, 1996), all of which contribute to increased pain after surgery. The underlying mechanisms that are responsible for the development of chronic postsurgical pain (CPSP) have yet to be determined. However, it is postulated that blocking or blunting peripheral and central sensitization may inhibit the processes that can lead to the development of CPSP (Costigan, et al., 2009). Therefore, the mechanisms of peripheral and central sensitization that may start out as protective may become maladaptive, the consequences of which can be deleterious and much more resistant to treatment (Costigan, et al., 2009).

Post-surgical pain arises from predominantly two distinct processes: nociception (C fibre and Aδ primary sensory neurons which respond to intense thermal or mechanical stimuli) (Woolf & Ma, 2007) and inflammation which is a consequence of trauma to peripheral tissues (i.e., detection of inflammation by nociceptors) (Costigan, et al., 2009). Dysfunctional pain, such as neuropathic pain that results from direct injury to the nervous tissue (e.g. nerve transection) (Kelly, Ahmad, & Brull, 2001), is also present in the acute postoperative period. While most neuropathic pain resolves with time (Kehlet, et al., 2006), in a subset of patients, the acute neural damage from surgery can transition to chronic neuropathic pain that is often resistant to treatment. These types of injuries can result in long-term changes in the sensitivity of the nervous system, such that the intensity of subsequent stimuli necessary to induce pain is reduced (i.e. lower pain threshold) (Woolf & Salter, 2000).
2.2 Evolution from Preemptive to Preventive Analgesia

2.2.1 Preemptive Analgesia

Preemptive analgesia has been defined as preoperative antinociceptive treatment that prevents the establishment of surgery-induced central sensitization and heightened postoperative pain intensity (Wall, 1988). The original design evaluating preemptive analgesia required two groups of patients that received identical treatment before or after surgery. Typically the only difference between the two groups was the timing of the administration of the analgesic agent relative to skin incision. By varying only the timing of the intervention, this paradigm assumes that the intraoperative nociceptive barrage contributes to a greater extent to central sensitization and postoperative pain than does the postoperative nociceptive barrage. The thought has been that patients who received treatment before surgery will have less pain than patients that received treatment after surgery.

This view of preemptive analgesia is too restrictive and narrow (Coderre, Katz, Vaccarino, & Melzack, 1993; Katz, 1995; Katz, Clarke, & Seltzer, 2011; Kissin, 1994a) in part because (1) the evidence indicates that sensitization is induced by factors other than the peripheral nociceptive barrage associated with incision and subsequent noxious intraoperative events, and (2) it is unclear the relative extent to which pre, intra, and postoperative peripheral nociceptive inputs contribute to central sensitization and postoperative pain.

The near exclusive focus in the literature on this narrow view of preemptive analgesia has had the unintended effect of diverting attention away from other clinically significant findings because they do not conform to what has become the accepted definition of preemptive analgesia (Katz & Clarke, 2008). The classic two group design does not allow for
other equally plausible alternatives that have received empirical support in the pain and anesthesia literatures (Gordon, Brahim, Dubner, McCullagh, Sang, & Dionne, 2002; Gundes, Kilickan, Gurkan, Sarlak, & Toker, 2000; Singh, Phillips, Kuo, & Campbell, 2007). The previous studies suggest that better pain relief may be achieved when the analgesic intervention is started after incision and potentially after surgery (i.e. in the context of an unchecked peripheral nociceptive injury barrage during surgery). Recently, the concept of preventive analgesia has replaced the emphasis that the narrow view of preemptive analgesia placed on the timing of analgesic administration.

2.2.2 Preventive Analgesia

A broader approach to the prevention of postoperative pain has evolved that aims to minimize the deleterious immediate and long-term effects of noxious perioperative afferent input (Katz & Clarke, 2008; J. Katz & C. J. McCartney, 2002). The focus of preventive analgesia is not on the relative timing of analgesic or anesthetic interventions, but on attenuating the impact of the peripheral nociceptive barrage associated with noxious preoperative, intraoperative, and/or postoperative events/stimuli. These stimuli induce peripheral and central sensitization, which increase postoperative pain intensity and analgesic requirements. Preventing sensitization will reduce pain and analgesic requirements. Preventive analgesia is demonstrated when postoperative pain and/or analgesic use are reduced beyond the clinical duration of action of the target agent which we have defined as 5.5 half lives of the target agent. This requirement ensures that the observed effects are not analgesic effects. (Katz, 1995; Katz & Clarke, 2008; McCartney, et al., 2004)

In Figure 2.1, the eight possible treatment combinations of giving or not giving analgesics across the three perioperative phases are illustrated.
**Figure 2.1** Schematic representation showing the administration (+) or non-administration (-) of pharmacological agents across the pre-operative, intraoperative and post-operative phases of surgery, yielding 8 different treatment combinations and 28 possible two-group designs to evaluate the efficacy of preemptive and preventive analgesia. Reprinted with permission from Katz, Clarke and Seltzer, 2011.

The preoperative phase encompasses interventions that begin days before surgery, up to those administered just minutes before skin incision. The intraoperative phase includes interventions started immediately after incision to those initiated just before the end of surgery (e.g., skin closure). The postoperative phase includes interventions started immediately after the end of surgery and may extend days or weeks after hospital discharge. There is potential for considerable variation in the timing and duration of administration of
analgesic agents, especially within the preoperative and postoperative phases (Katz, et al., 2011). Evidence demonstrates that there are extensive differences among studies on when (and for how long) similar analgesic agents are given.

Only recently have clinical trials begun to examine the effects of perioperative interventions well beyond the surgical time period (i.e. looking for a preventive effect). Long-term follow-up of patients several weeks, months or years after surgical intervention is necessary to test for the preventive effects of a perioperative intervention.

2.3 Multimodal Analgesia

For many years, the primary modality used for postoperative pain has been opioid-based analgesia. However, the side effects of opioid-based analgesics which include nausea, vomiting, sedation, pruritus, constipation, urinary retention, respiratory depression often impair patient progress and recovery after surgery (Strassels, McNicol, & Suleman, 2005). The increased morbidity associated with opioid only strategies, and the evidence that opioid medications tend not to be effective at relieving movement evoked pain, have created a movement in anesthesiology to adopt multimodal analgesic strategies to manage preoperative, intra-operative, and postoperative pain. These multimodal strategies are often implemented throughout the perioperative (i.e. the three time periods of the hospital stay: preoperative, intra-operative, and postoperative) stay.

2.3.1 Definition

With the advances in the understanding of the pathophysiology of pain, multimodal analgesia has become the standard of practice to treat moderate to severe postsurgical pain following orthopedic surgery (Joshi, 2005). This practice involves the use of different classes of
analgesic agents with different routes of administration to: [1] provide superior pain relief at rest and with movement, [2] reduce opioid consumption, and [3] reduce analgesic-related adverse effects (Brown, Christo, & Wu, 2004; Joshi, 2005). Many clinical trials have demonstrated the effectiveness of multimodal analgesia, however, positive results have not been routinely translated into clinical practice (Hsieh & Yealy, 2005; Marshall, 2006). Although single-agent therapy may attenuate central nociceptive processing, multimodal analgesic therapy is more effective, and is often associated with fewer side effects compared with high-dose, single-agent opioid therapy (Gilron, Bailey, Tu, Holden, Weaver, & Houlden, 2005a; Moiniche, Hjortso, Hansen, Dahl, Rosenberg, Gebuhr, & Kehlet, 1994). As discussed below, empirical evidence derived from clinical trials shows the use of multimodal analgesic therapy using a combination of analgesic agents, each with different mechanisms of action, is effective in blocking the various inputs/receptors related to the neural and inflammatory processes (Barrington, Olive, McCutcheon, Scarff, Said, Kluger, Gillett, & Choong, 2008; Clarke, et al., 2009b; Hebl, Dilger, Byer, Kopp, Stevens, Pagnano, Hanssen, & Horlocker, 2008; Horlocker, Kopp, Pagnano, & Hebl, 2006). The results of two recent studies have shown good acute pain control with the use of multimodal pain regimens after total hip or knee joint arthroplasty (Clarke, et al., 2009a; Clarke, et al., 2009b). Multimodal pain regimens of gabapentin, non-steroidal anti-inflammatories (eg. celecoxib), acetaminophen and regional anesthesia were effective in controlling perioperative pain and decreasing perioperative opioid use (Clarke, et al., 2009a; Clarke, et al., 2009b). More data are needed to determine whether similar multimodal pain regimens with regional anesthesia (an anesthetic that affects a large part of the body (i.e. a limb), which is often achieved with central-neuraxial anesthesia (i.e. spinal/epidural anesthesia) and/or peripheral nerve blocks)
reduce the time course of recovery, and/or maximize functional recovery of patients following major surgery.

2.3.2 Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)

The analgesic effects of NSAIDs have been attributed to their anti-inflammatory properties with respect to inhibiting the synthesis of prostaglandins (Yaksh, Dirig, & Malmberg, 1998). Prostaglandin (PG) synthesis is essential for the generation of inflammatory pain and this depends not only on prostaglandin production at the site of inflammation, but also on the actions of prostaglandins synthesized within the central nervous system. Prostaglandins derive from arachidonic acid liberated from phospholipids in the cell membrane by the action of phospholipase A$_2$ (PLA$_2$) enzymes (Samad, Sapirstein, & Woolf, 2002). Cyclooxygenase (COX) catalyzes the first two reactions of the PG pathway. The identification of two COX isoforms, COX-1 and COX-2, led to intense efforts to characterize the relative contribution of each isoform to prostaglandin production in specific situations (Samad, et al., 2002), and to the development of specific COX-2 selective inhibitors as COX-2 is an enzyme responsible for inflammation and pain.

Findings that the inflammatory cascade caused by tissue injury can be decreased in the periphery and blunted at the level of the spinal cord have increased the use of NSAIDs as an adjunct for the treatment of postoperative pain (Forrest, Camu, Greer, Kehlet, Abdalla, Bonnet, Ebrahim, Escolar, Jage, Pocock, Velo, Langman, Bianchi, Samama, & Heitlinger, 2002; Kehlet & Dahl, 1992). Oral and intravenous (i.v.) bioavailability of NSAIDs is higher than that of rectal administration, thus the former routes of administration are preferred postoperatively (Tramer, Williams, Carroll, Wiffen, Moore, & McQuay, 1998). However, NSAIDs are not widely used because of their potential adverse effects; including gastric
ulceration or hemorrhage, renal dysfunction and platelet inhibition. It is clear that NSAIDs should be used with caution in patients that have a history of renal dysfunction, sepsis, end-stage liver disease or cardiac disease. Evidence has demonstrated that the short term use of nonselective NSAIDs (e.g. Ketoprofen/ Ibuprophene) is safe with respect to the gastrointestinal complications (Derry, Derry, Moore, & McQuay, 2009; Rapoport, 1999). In terms of bone repair, studies based on animal models postulated a link between impaired bone fusion and the use of NSAIDs (Gerstenfeld, Thiede, Seibert, Mielke, Phippard, Svagr, Cullinane, & Einhorn, 2003). Clinical data has not supported such a link (Buvanendran, Kroin, Tuman, Lubenow, Elmofty, Moric, & Rosenberg, 2003; Huang, Wang, Wang, Lin, Horng, & Jiang, 2008; Meunier, Aspenberg, & Good, 2009). A two year randomized study demonstrated that a three week postoperative regimen of celecoxib did not affect prosthesis fixation after total knee replacement (Meunier, et al., 2009). More studies examining the safety of NSAIDs are needed to evaluate the effects of reducing the inflammatory process on other tissues, such as muscle and tendon repair, as well as functional outcomes following arthroplasty surgery. While it seems logical that resolution of inflammation should improve the tissue repair processes, there is conflicting evidence from animal models of skeletal muscle and tendon injury and repair which challenge the notion that prolonged use of anti-inflammatories, particularly beyond the acute inflammatory phase is beneficial (Lapointe, Fremont, & Cote, 2002, 2003; Marsolais, Cote, & Frenette, 2003). The prolonged blockade of inflammation by nonselective NSAIDs throughout the perioperative period and beyond, demonstrated an increase in rearing (standing on hind limbs) and ambulatory behaviour of rats 1-3 days post knee surgery (Lapointe, et al., 2003). The increased spontaneous activity level in rats suggests the blockade was effective. Whether these results will be similar in humans remains unknown.
COX-2 selective inhibitors have been developed to target the COX-2 enzyme while sparing the COX-1 enzyme. The only available COX-2 agent in North America is Celecoxib. Studies suggest that COX-2 selective inhibitors have similar analgesic effects as nonselective NSAIDs but they do not affect platelet function. This reduces the risk of perioperative bleeding and means that COX-2 selective inhibitors can safely be given preoperatively (Buvanendran, et al., 2003; Gajraj & Joshi, 2005; Gilron, Milne, & Hong, 2003; Romsing & Moiniche, 2004). Of particular importance in the arthroplasty population, COX-2 selective inhibitors do not inhibit bone healing (Gajraj, 2003). However, their effects on muscle tissue and connective tissue healing, which are important for regaining full function postoperatively, remain unknown.

The choice of NSAID (i.e. nonselective or COX-2 specific) will often be determined by factors such as available pharmaceutical formulations, cost, and patient tolerability. In the postoperative setting, the addition of an NSAID to a postsurgical regimen is often influenced by the severity of the acute pain. Arthroplasty pain has been well described as being moderate to severe in the acute 48 hour postsurgical time period (Goldstein, Ellis, Brown, Wilson, Penning, Chisom, & VanDenKerkhof, 2004). The selective COX-2 inhibitors continue to demonstrate a good analgesic and anti-inflammatory profile (Jones & O'Donnell, 2008), while sparing the non-desirable effects of the COX-1 agents. Celecoxib seems to be an ideal adjunct within postsurgical multimodal analgesic regimens after orthopedic and other major surgery.

2.3.3 Acetaminophen

Acetaminophen is a widely used analgesic and antipyretic drug that is available without prescription. It is a remarkably safe drug that is often used for mild to moderate pain (Toms,
Derry, Moore, & McQuay, 2009). The most common indications are for headache, migraine, fever, menstrual pain, toothache, dental pain, muscular and joint pains, and neuralgia (Damen, Bruijn, Verhagen, Berger, Passchier, & Koes, 2005; Di Girolamo, Sanchez, De Los Santos, & Gonzalez, 2004; Duggan & Scott, 2009; Southey, Soares-Weiser, & Kleijnen, 2009). The anti-inflammatory effects of acetaminophen are much weaker than the NSAIDs (Hinz & Brune, 2007). Acetaminophen lacks antirheumatic effects, presumably reflecting the modest peripheral inhibiting effect on prostaglandin synthesis produced by this drug (Towheed, Judd, Hochberg, & Wells, 2003; Zhang, Jones, & Doherty, 2004). Conversely, acetaminophen inhibits the action of endogenous pyrogens on the heat-regulating centers in the brain by blocking the formation and release of prostaglandins in the central nervous system (Anderson, 2008). Some researchers postulate an entirely different central mechanism of action (i.e. a COX-3 pathway). The COX-3 pathway would strongly inhibit central prostaglandin synthesis in the hypothalamus and decrease prostaglandin E in cerebrospinal fluid, ultimately producing the analgesic and antipyretic effects (Botting & Ayoub, 2005; Chandrasekharan, Dai, Roos, Evanson, Tomsik, Elton, & Simmons, 2002; Rezende, Franca, Menezes, dos Reis, Bakhle, & Francisch, 2008). There is ongoing research to elucidate the COX-3 mechanism of action of acetaminophen.

Although acetaminophen has a very good safety profile, overdoses, either deliberate or accidental, are not uncommon. The recommendation is that adults or children over 12 years of age can be given 500mg to 1g of acetaminophen every 4-6 hours up to a maximum of 4g in any 24 hour period. Adverse events rarely occur within therapeutic doses, although there have been reports of increased liver enzymes with long term use at the higher doses (Larson, 2007).
Two systematic reviews have demonstrated the beneficial effects of acetaminophen vs. placebo to treat postoperative pain (Barden, Edwards, Moore, & McQuay, 2004; Moore, Collins, Carroll, & McQuay, 1997). Using a dose response study, McQuay and Moore demonstrated that 1g of acetaminophen produced greater benefits than a 600/650-mg dose with a number needed to treat (NNT) of 9 (McQuay & Moore, 2007). The NNT when combined with codeine decreases to 2.2 (McQuay & Moore, 2007). One systematic review that compared acetaminophen vs. NSAIDS revealed mixed results (Wienecke & Gotzsche, 2004). The authors concluded that the treatment of postoperative pain was superior when the agents were combined than when either single agent was administered alone. Acetaminophen’s efficacy in treating mild to moderate pain combined with its relatively benign side effect profile (no gastric irritation or platelet aggregation effects), is why it continues to be widely used as part of postoperative multimodal pain regimens.

2.3.4 Local Anesthesia

An ophthalmologist from the Czech Republic, Dr. Karl Koller, was the physician credited with the first use of cocaine as a local anesthetic solution in 1884. Today, the use of local anesthesia continues to be a very important adjunct to decrease pain, opioid consumption, and opioid related side effects (Dahl, Moiniche, & Kehlet, 1994). Regional anesthesia (which utilizes local anesthetic solutions) is an integral part of orthopedic anesthesia practice. As part of anesthetic care, local anesthetics have been shown to facilitate early mobilization and discharge (Kasibhatla & Russon, 2009; Kerr & Kohan, 2008). Local anesthetic solutions, (for example; bupivacaine and lidocaine) are commonly used neuraxially (spinal/epidural) and have become popular in some centres with respect to intra-articular use.
Spinal/epidural anesthesia has become the anesthetic modality of choice in centres that specialize in lower limb arthroplasty. Such centres have developed specialized areas where patients receive their surgical anesthesia (spinal/epidural) and peripheral nerve blocks (femoral and/or sciatic nerve blocks/catheters) prior to entering the operating room. This is one of the factors that enabled increased surgical volumes and decreased surgical wait times in Ontario (Ontario Ministry of Health and Longterm Care, 2009). Prior to implementation of these specialized pre-operative pain management areas, anesthesiologists were challenged to prepare patients undergoing orthopedic procedures with the appropriate regional anesthesia block, often due to operating room time pressures. The addition of specialized preoperative anesthesia block areas has increased the availability of intrathecal/spinal anesthesia and regional anesthesia blocks for use with patients undergoing major orthopedic surgery. The mandate to reduce wait times and increase surgical volumes has also served as the impetus for closer collaboration between anesthesiologists, physical therapists, nurses and surgeons to optimize efficiency while maintaining safe mobilization of patients undergoing total hip or knee replacement.

Local anesthetics injected into the intra-articular space have been shown to improve pain scores, reduce opioid consumption, facilitate functional recovery and mobilization after knee arthroscopy (Moiniche, Mikkelsen, Wetterslev, & Dahl, 1999). Although the duration of pain relief may be shorter than with peripheral nerve catheters and neuraxial analgesia, this technique may play a larger role in ambulatory orthopedic day surgeries (e.g. arthroscopy). Ongoing studies are investigating the effectiveness of intra-articular injections for patients with total hip and knee joint arthroplasty.
2.3.5 Regional Anesthesia after Lower Limb Musculoskeletal Surgery

2.3.5.1 Single Injection Peripheral Nerve Blocks

Femoral and sciatic nerve blocks remain very popular after total knee arthroplasty (Allen, Liu, Ware, Nairn, & Owens, 1998; Ben-David, Schmalenberger, & Chelly, 2004). The femoral nerve innervates the anterior compartment of the knee while the sciatic nerve innervates the posterior compartment. In patients that receive only femoral nerve blocks, posterior knee compartment pain can be problematic leading some clinicians to recommend that both blocks provide superior pain relief after total knee arthroplasty (Ben-David, et al., 2004). For foot and ankle surgery, popliteal fossa nerve blocks (which target the sciatic nerve as it passes below the knee) provide analgesic success with minimal side effects (Enneking, Chan, Greger, Hadzic, Lang, & Horlocker, 2005). The duration of neural blockade can be quite variable. Block duration is determined by the properties of the local anesthetic used, the concentration of the local anesthetic, and the volume injected. A longer acting solution of Ropivacaine 0.5%, 20 mL, deposited adjacent to each nerve will produce a mean anesthetic duration of action of 15 hours (Weber, Fournier, Riand, & Gamulin, 2005). Occasionally it becomes difficult to predict the level of motor impairment that accompanies single injection nerve blocks. This is a substantial consideration for patient safety if ambulation on postoperative day 0, or early on postoperative day 1, is desirable. The inability to accurately predict the density of neuronal blockade that will be experienced by patients (i.e. a good sensory nerve block with minimal motor impairment) is the reason that continuous peripheral nerve catheters have increased in popularity and use.
2.3.5.2 Continuous Peripheral Nerve Catheters

By placing a catheter in the perineural space, the duration of analgesia can be prolonged and the density of the block better managed by infusion of the anesthetics (Boezaart, 2006; Evans, Steele, Nielsen, Tucker, & Klein, 2005). When compared directly to intravenous patient controlled anesthetic (PCA), most studies have demonstrated superior pain relief at rest and with movement, better postoperative knee flexion, and earlier discharge (Capdevila, Barthelet, Biboulet, Ryckwaert, Rubenovitch, & d'Athis, 1999; Singelyn, Deyaert, Joris, Pendeville, & Gouverneur, 1998). Unfortunately, the increased cost and lack of expertise in placing peripheral nerve catheters often limits their use. Whenever peripheral nerve techniques are used (either single injection or catheters) it is very important that anesthesiologists and physiotherapists engage in dialogue in order to reach rehabilitation goals and avoid the delay in functional recovery that can be caused by dense motor blockade.
Chapter 3

Objectives & Hypotheses

3.1 Objectives

The objectives of this dissertation are the following: 1) to determine whether or not perioperative administration of gabapentin reduces postoperative opioid consumption and postoperative pain scores 2) to determine whether or not adding a single 600 mg dose of gabapentin either before or after surgery within the context of spinal anesthesia and a robust multimodal analgesia regimen reduces acute pain and the incidence and intensity of chronic postsurgical pain 6 months after surgery 3) to examine the efficacy of using gabapentin for the treatment of pre-operative anxiety.

3.2 Specific Questions

1. Does adding gabapentin to a multimodal perioperative analgesic regimen reduce opioid consumption and increase functional recovery after total knee arthroplasty compared to patients that received placebo medication?

2. Does a single 600 mg dose of gabapentin reduce pain scores and decrease opioid consumption after total hip arthroplasty using a multimodal analgesic regimen including spinal anesthesia?

3. Is preoperative administration of gabapentin 600 mg more effective than postoperative administration at reducing postoperative pain and opioid consumption?

4. Does 600 mg of gabapentin given prior to surgery reduce preoperative anxiety prior to total hip arthroplasty compared to patients that received placebo medication?
5. Does 1200 mg of gabapentin reduce preoperative anxiety in moderate to highly
anxious female patients undergoing major surgery compared to patients that received
placebo medication?

3.2 Hypotheses

The specific hypotheses for each study are outlined. The data analyses are described in detail
in the Methods section of each chapter.

Study 1 (Chapter 4), Gabapentin Decreases Morphine Consumption and Improves Functional
Recovery following Total Knee Arthroplasty (Clarke et al. *Pain Research and Management*,

Specific Hypotheses:

1. Patients continued on gabapentin postoperatively will require less opioid pain
medication compared to patients that receive placebo medication.

2. Patients receiving postoperative gabapentin will have improved function while
performing physiotherapy tasks (i.e. active assisted knee flexion).

Study 2 (Chapter 5), Gabapentin Added to a Multimodal Regimen with Spinal Anesthesia
does not Reduce Acute Pain, Opioid Consumption or Chronic Pain up to Six Months after

Specific Hypotheses:
1. A single 600 mg dose of gabapentin added to a robust multimodal analgesic regimen will reduce opioid consumption, acute pain scores and decrease the incidence and severity of chronic postsurgical pain 6 months after surgery.

2. Preemptive administration of gabapentin 600 mg will be superior to postoperative administration of the same dose.

Study 3 (Chapter 6), Gabapentin does not Reduce Preoperative Anxiety When given Prior to Total Hip Arthroplasty (Clarke et al. Pain Med, 11(6), 966-971 (2010))

Specific Hypothesis:

1. Patients that receive gabapentin 600 mg prior to total hip arthroplasty will report a greater reduction in pre-operative anxiety compared to patients that received placebo medication.

Study 4 (Chapter 7), Gabapentin Reduces Preoperative Anxiety and Pain Catastrophizing in Highly Anxious Patients Prior to Major Surgery. (Clarke et al. Canadian Journal of Anesthesia, accepted for publication (May 2013))

Specific Hypotheses:

1. Patients with moderate to high levels of preoperative anxiety that are given 1200 mg of gabapentin prior to surgery will report a greater reduction in pre-operative anxiety prior to major surgery compared with patients that received placebo medication.
2. Patients given gabapentin 1200 mg compared with a placebo will have lower scores on the Pain Catastrophizing Scale, the Pain Anxiety Symptoms Scale and report higher levels of perioperative sedation.
Chapter 4

Study 1

By the year 2000, the use of gabapentin as an anticonvulsant had become supplanted by its use in the treatment of patients with chronic neuropathic pain conditions. Furthermore, anesthesiologists had begun to highlight the potential benefit of using gabapentin as an adjunctive anesthetic medication. Prior to this study being designed, 12 studies examining the effects of gabapentin on postoperative pain (see Section 4.2) had been published. Of these, 8 had used differing doses of gabapentin preoperatively and had reported the effects on postoperative pain scores and opioid consumption. The preemptive dose of gabapentin had been evaluated in a dose-response study (Section 4.2). The optimal preoperative dose for patients undergoing lumbar discectomy was suggested to be 600 mg; at higher doses (900 and 1200 mg) an analgesic ceiling effect was observed in which patients exhibited more side effects with no additional reduction in pain.

Many questions remained unanswered with respect to the use of gabapentin in other surgical models. Having reviewed the current literature, we designed a pilot study (Chapter 4) with the aim to determine an appropriate perioperative dosing regimen after postoperative TKA. Since many of the gabapentin trials published to this point had demonstrated a significant reduction in movement evoked pain we hypothesized that continuing gabapentin into the rehabilitation period would lead to decreased pain during rehabilitation treatments and to improved functional recovery (i.e., greater range of motion).

Study 1 was published in Pain Research and Management 2009; 14 (3):217-22, and permission to reproduce this manuscript has been obtained from the publisher. This study was also presented at the Canadian Anesthesiology Society Annual Meeting in Calgary, Alberta, Canada, 2007.
4 Gabapentin Decreases Morphine Consumption and Improves Functional Recovery Following Total Knee Arthroplasty

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4.1 Abstract

Background: After total knee arthroplasties (TKA), moderate to severe pain often interferes with postoperative rehabilitation and delays discharge from hospital. This study examined the effects of a 4 day postoperative gabapentin (GBP) vs placebo intervention on opioid consumption, pain scores, knee flexion and adverse effects after TKA.

Methods: After obtaining REB approval and informed consent, 40 patients were enrolled in a randomized, single-blind, placebo-controlled, open label study. Patients were assigned to one of five groups: Preop Placebo/ Postop Placebo (G1), Preop GBP 600 mg/ Postop Placebo (G2), Preop GBP 600 mg/ Postop GBP 100 mg TID (G3), Preop GBP 600 mg/ Postop GBP 200 mg TID (G4), Preop GBP 600 mg/ Postop GBP 300 mg TID (G5). Postop GBP or placebo was continued for 4 days after surgery. Two hours prior to surgery all patients received celecoxib 400 mg. Based on the above groupings, patients in G1 received placebo medication, whereas patients in G2, G3, G4, and G5 received gabapentin 600 mg 2 hours preoperatively. All patients received femoral and sciatic nerve blocks, followed by spinal anesthesia. Beginning in the PACU, all patients received a postoperative regimen of celecoxib 200 mg q12h for four days and a PCA morphine pump for 48 hrs.
Results: 36 patients (G1 (n=7), G2 (n=7), G3 (n=8), G4 (n=7), G5 (n=7)) completed the study. Data were analyzed by one-way ANOVA followed by a contrast comparing patients that received postoperative GBP (G3, G4, & G5) (n=22) to patients that received placebo postoperatively (G1, G2) (n=14). Patients that received GBP postoperatively used significantly less PCA morphine at 24 hrs, 36 hrs and 48 hrs (p <0.05). The postoperative GBP patients had significantly better active assisted knee flexion on POD 2, POD 3, with a trend toward better flexion on POD 4. Patients that received GBP postoperatively reported less pruritus than patients that received placebo. There were no differences in pain scores.

Conclusions: These results support the use of GBP in the acute postoperative period. Further trials are needed to delineate the optimal dose, timing and duration of gabapentin use following surgery.

4. 2 Introduction

Over 430,000 Total Knee Arthroplasties (TKA) are performed in North America each year. In Canada over 30,000 TKAs are performed annually with many patients experiencing moderate to severe postoperative pain (Cremeans-Smith, Boarts, Greene, & Delahanty, 2009; Fischer, Simanski, Sharp, Bonnet, Camu, Neugebauer, Rawal, Joshi, Schug, & Kehlet, 2008) which interferes with postoperative rehabilitation, subsequent discharge from hospital and leads to the development of chronic pain in 30% of patients (Goldstein, et al., 2004). Standard perioperative pain management often relies on opioids as the primary pain medication, but they are relatively ineffective for severe movement associated pain and are associated with significant side effects such as nausea, vomiting, sedation, pruritus, constipation, urinary retention and respiratory depression (Strassels, et al., 2005). The preoperative use of a non-opioid medication, gabapentin (GBP), has been shown to be
effective in reducing opioid use and accelerating functional recovery for 48h after anterior cruciate ligament repair (Menigaux, et al., 2005).

Much more work needs to be done with regard to the optimal dosing of gabapentin in various surgical populations and the determination of this medication’s efficacy at treating postoperative pain beyond the immediate 24 or 48 hours of surgery. Since many of the gabapentin trials published to this point have demonstrated a significant reduction in movement evoked pain (Al-Mujadi, et al., 2006; Dirks, et al., 2002; Fassoulaki, et al., 2005b; Gilron, et al., 2005b; Menigaux, et al., 2005; Rorarius, et al., 2004; Turan, et al., 2006b) we hypothesized that continuing gabapentin into the rehabilitation period would lead to decreased pain during rehabilitation treatments and to improved functional recovery (i.e., greater range of motion).

There are several novel aspects to the present study: (1) This is the first trial to examine the effect of gabapentin in patients undergoing TKA. (2) This is the first trial to use neuraxial regional anesthesia as the primary anesthetic modality. Until Turan’s (Turan, White, Karamanlioglu, & Pamukcu, 2007) recent study demonstrating that premedication with oral gabapentin (1.2 g) decreased tourniquet-related pain and improved the quality of anesthesia during hand surgery under intravenous regional anesthesia (Turan, et al., 2007), all other studies have used general anesthesia with volatile agents as the main anesthetic technique. (3) Furthermore, in the present study gabapentin is administered for four days after surgery in order to determine whether this medication helps to improve functional outcomes in the acute hospital rehabilitation period. Menigaux found that a single dose of gabapentin 1200 mg preoperatively improved first and maximal passive and active knee flexions at 24 and 48 hours in the gabapentin group compared to the control group (Menigaux, et al., 2005).
The concept of multimodal analgesia involves the use of different classes of analgesic agents with different routes of administration (1) to provide superior pain relief at rest and after movement, and to reduce (2) opioid consumption, and (3) analgesic-related adverse effects (Brown, et al., 2004; Joshi, 2005). Although many clinical trials demonstrate the effectiveness of multimodal analgesia, positive results may not translate into clinical practice (Hsieh & Yealy, 2005; Marshall, 2006). One reason may be that comparing a treatment to a placebo lacks clinical applicability. In order to adequately treat pain in the perioperative period, multimodal treatments which target the multiple cellular mechanisms that trigger the pain response must be compared with a clinically relevant control condition. The present study was designed to evaluate the efficacy of gabapentin in the context of a clinically relevant, multimodal regimen including preoperative spinal anesthesia (bupivacaine), non-steroidal anti-inflammatories (NSAIDS-celecoxib), and peripheral femoral and sciatic nerve blocks (with ropivacaine).

4.3 Methods
The study was approved by the hospital Research Ethics Board and all patients gave informed, written consent to participate. Patients between the age of 18-75 with an ASA physical status score of I or II undergoing TKA were eligible for this study. Patients were not eligible if they had a known allergy to any of the medications being used, a history of drug or alcohol abuse, a history of being on chronic pain medications (i.e. slow-release preparations of opioids given that morphine consumption was our primary outcome), a history of being on gabapentin or pregabalin, rheumatoid arthritis, a psychiatric disorder, a history of diabetes with impaired renal function, a body mass index of greater than 40 or were unable or unwilling to use Patient Controlled Analgesia (PCA).
Patients were recruited at their pre-operative assessment visit approximately 1-2 weeks in advance of their surgery. All subjects were screened and the study protocol, the use of the PCA pump, and a 10 cm visual analogue scale (VAS) for pain measurement (with endpoints “no pain” and “worst pain possible”) were explained. A computer generated randomization schedule was used to assign patients at random in blocks of five to one of the treatment groups. The schedule was created by the hospital investigational pharmacy which was otherwise not involved in the clinical care of the patients or in the conduct of the trial. On the day of surgery, patients were randomly assigned to one of five treatment arms: Preoperative Placebo/ Postoperative Placebo (G1), Preoperative GBP 600 mg/ Postoperative Placebo (G2), Preoperative GBP 600 mg/ Postoperative GBP 100 mg TID (G3), Preoperative GBP 600 mg/ Postoperative GBP 200 mg TID (G4), Preoperative GBP 600 mg/ Postoperative GBP 300 mg TID (G5). Two hours prior to surgery all patients received celecoxib 400 mg. Based on the above groupings, patients in G1 received placebo medication, whereas patients in G2, G3, G4, and G5 received gabapentin 600 mg 2 hours preoperatively. Postoperative GBP or placebo was continued for 4 days after surgery beginning 8 hours after the preoperative dose.

All patients were prepared for surgery in a specialized block area. An intravenous infusion of Lactated Ringer’s solution was started after insertion of an 18 g intravenous cannula. Blood pressure, ECG and oximetry monitors were applied. Midazolam 1-3 mg i.v. was administered to achieve anxiolysis. Femoral and sciatic nerve blocks were performed using a nerve stimulator/ultrasound technique to localize the nerves at less than 0.5 ma. Ropivacaine 0.5%, 20 mL, with an approximate mean duration of action of 15 hours, was deposited adjacent to each nerve (Weber, et al., 2005). Spinal anesthesia was performed in the lateral decubitus or sitting position. After subcutaneous infiltration with lidocaine 1%, and using a midline approach, a 25 gauge Whitacre needle was inserted at the L3-4, L4-5, or L5-S1 interspace, with the
aperture directed to the side of surgery. When free flow of CSF was obtained, 10 mg of 0.5% hypobaric bupivacaine with 10 micrograms of fentanyl was injected. In all groups, total volume injected to the subarachnoid space was 2.2 mL, with aspiration at the end of injection to ensure that all of the drug was injected intrathecally. The patient was then placed in the lateral decubitus position with the side of surgery uppermost. Patients were then transferred to the operating room where monitors were reapplied, supplemental oxygen was provided, and sedation was provided by an intravenous propofol infusion (25-100 mcg/kg/min) until the end of surgery. The attending anesthesiologist was not involved in the patients’ evaluation postoperatively.

Beginning postoperatively in the PACU, all patients, regardless of treatment group, received a standard postoperative regimen of celecoxib 200 mg q12h for four days and an intravenous PCA morphine pump.

VAS pain scores at rest were obtained at the time of PCA hook up in the PACU (0 hr) and every 4 hours collected by the Holland Orthopedic and Arthritic nursing staff (who had no investment in the study) for the following 48 hours. All pain scores in this study were measured with patients in a resting position. The PCA pump was set to deliver a 1 mg bolus of morphine per demand with a five minute lockout and no background infusion. All patients were instructed to maintain their VAS pain score less than 4/10. If the VAS pain score was 5 or greater at rest on two consecutive pain assessments, the dose of i.v. PCA morphine was increased to 1.5 mg per demand. In addition, at each 4-hour time point, the incidence and severity of sedation, nausea, vomiting, and pruritus were assessed.

Postoperatively all patients followed a Primary Knee Replacement Care Pathway, accompanied by a standardized rehabilitation treatment protocol. All patients began a full
weight bearing regimen and participated in a progressive program of range of motion, strengthening exercises, balance and ambulation beginning the first day after surgery. On postoperative days 2, 3 and 4, active assisted knee flexion range of motion was assessed for all patients by a qualified physiotherapist. Degrees of motion were recorded using a standard long-arm goniometer. The goniometer was centered on the axis point of the knee with the proximal reference point being the greater trochanter at the hip and the distal reference point, the lateral malleolus at the ankle. Active-assisted knee flexion was measured with the patient in a sitting position with a towel placed under the proximal thigh. Following standard treatment, patients were asked to bend their knee as far back as possible at which point the therapist applied overpressure and recorded the measurement in degrees. Assessment of knee range of motion in patients with knee OA has been shown to have good reliability (Kennedy, et al., 2005).

Upon completion of this study, the data were entered into the statistical software package SPSS 15.0 (Chicago, IL, USA). We lack an a priori sample size calculation for this study because the aim of this work was to generate data for a larger study. Demographic and clinical variables were compared among the groups using one way ANOVA or chi-squared test as appropriate. Pain scores and morphine consumption were analyzed by ANOVA for repeated measures. Due to the small numbers of patients recruited in each group, we calculated a contrast comparing patients that received postoperative gabapentin (G3, G4, & G5) to patients that received postoperative placebo (G1, G2). This was also performed using an ANOVA for repeated measures. The degrees of active assisted knee flexion were compared using unpaired t tests. Finally, Mann-Whitney U non-parametric tests were performed to determine whether there was an association between adverse effects and study group assignment. A value of p < 0.05 was considered statistically significant.
4.4 Results

A total of 64 patients were approached and screened for interest in participating in this study. Twenty four patients declined to participate in the study, while the other forty patients were successfully recruited into the study. Four patients refused to complete the medication regimen and requested to be withdrawn from the study. Thus, 36 patients completed the study: 7 patients in group 1 (G1), 7 in group 2 (G2), 8 in group 3 (G3), 7 in group 4 (G4), and 7 in group 5 (G5). We used a protocol compliant approach to data analysis. The groups were comparable with respect to age, body mass index, gender and duration of surgery (Table 4.1).

Table 4.1 Demographic Characteristics and Duration of Surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>(G1) Placebo/Placebo (n=7)</th>
<th>(G2) GBP 600/Placebo (n=7)</th>
<th>(G3) GBP 600/GBP 100 (n=8)</th>
<th>(G4) GBP 600/GBP 200 (n=7)</th>
<th>(G5) GBP 600/GBP 300 (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>60.7 ± 6.6</td>
<td>63.9 ± 5.6</td>
<td>57.3 ± 7.4</td>
<td>65.8 ± 6.5</td>
<td>62.33 ± 6.6</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>3/4</td>
<td>2/5</td>
<td>4/4</td>
<td>3/4</td>
<td>2/5</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>31.0 ± 8.5</td>
<td>34.2 ± 6.1</td>
<td>28.1 ± 4.1</td>
<td>29.5 ± 3.6</td>
<td>28.0 ± 2.2</td>
</tr>
<tr>
<td>Duration of Surgery</td>
<td>77.0 ± 20.3</td>
<td>58.2 ± 17.2</td>
<td>63.3 ± 25.7</td>
<td>68.2 ± 27.0</td>
<td>65.8 ± 27.0</td>
</tr>
</tbody>
</table>

Overall, significant differences among groups (G1 - G5) were not found in mean morphine consumption or pain scores (Table 4.2 & Table 4.3).
Table 4.2 Cumulative Morphine Consumption (mg) after Surgery

<table>
<thead>
<tr>
<th>Hours after surgery</th>
<th>(G1) Placebo/Placebo (n=7)</th>
<th>(G2) GBP 600/Placebo (n=7)</th>
<th>(G3) GBP 600/GBP 100 (n=8)</th>
<th>(G4) GBP 600/GBP 200 (n=7)</th>
<th>(G5) GBP 600/GBP 300 (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 hours</td>
<td>19.71 ± 14.6</td>
<td>15.6 ± 8.4</td>
<td>18.5 ± 8.4</td>
<td>10.3 ± 6.5</td>
<td>11.1 ± 9.4</td>
</tr>
<tr>
<td>24 hours</td>
<td>63.8 ± 36.5</td>
<td>38.4 ± 23.8</td>
<td>38.2 ± 21.0</td>
<td>29.7 ± 20.9</td>
<td>25.8 ± 18.6</td>
</tr>
<tr>
<td>36 hours</td>
<td>91.2 ± 59.9</td>
<td>61.7 ± 41.0</td>
<td>60.2 ± 19.1</td>
<td>44.5 ± 24.6</td>
<td>42.2 ± 21.3</td>
</tr>
<tr>
<td>48 hours</td>
<td>95.2 ± 59.7</td>
<td>104.4 ± 17.2</td>
<td>73.4 ± 28.8</td>
<td>54.0 ± 35.7</td>
<td>44.0 ± 20.2</td>
</tr>
</tbody>
</table>

Data are mean ± SD. No significant differences were observed among groups.

Table 4.3 Mean VAS Rest Pain Scores after Surgery

<table>
<thead>
<tr>
<th>Hours after surgery</th>
<th>(G1) Placebo/Placebo (n=7)</th>
<th>(G2) GBP 600/Placebo (n=7)</th>
<th>(G3) GBP 600/GBP 100 (n=8)</th>
<th>(G4) GBP 600/GBP 200 (n=7)</th>
<th>(G5) GBP 600/GBP 300 (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In PACU</td>
<td>13.9 ± 26.7</td>
<td>0.28 ± 0.7</td>
<td>0.0 ± 0.0</td>
<td>11.0 ± 20.0</td>
<td>0.1 ± 0.4</td>
</tr>
<tr>
<td>12 hours</td>
<td>38.7 ± 28.5</td>
<td>33.1 ± 27.5</td>
<td>24.5 ± 38.2</td>
<td>17.7 ± 22.0</td>
<td>11.3 ± 5.8</td>
</tr>
<tr>
<td>24 hours</td>
<td>51.0 ± 21.8</td>
<td>41.7 ± 24.8</td>
<td>29.8 ± 20.4</td>
<td>29.5 ± 30.1</td>
<td>45.6 ± 29.2</td>
</tr>
<tr>
<td>36 hours</td>
<td>36.4 ± 19.5</td>
<td>45.0 ± 21.3</td>
<td>36.4 ± 26.4</td>
<td>29.3 ± 29.6</td>
<td>34.5 ± 22.8</td>
</tr>
<tr>
<td>48 hours</td>
<td>18.7 ± 22.8</td>
<td>17.8 ± 18.2</td>
<td>17.0 ± 18.2</td>
<td>10.0 ± 9.7</td>
<td>9.0 ± 7.3</td>
</tr>
</tbody>
</table>

Data are mean ± SD. No significant differences were observed among groups. PACU = Post Anesthetic Care Unit
However, a planned contrast comparing patients that received postoperative gabapentin (G3, G4, & G5) (n=22) to patients that received placebo medications postoperatively (G1, G2) (n=14) found significant differences. Demographic data were similar between the two contrasted groups (Table 4.4).

**Table 4.4 Demographic Characteristics for Postoperative Gabapentin versus Placebo Treated Patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Postoperative Placebo (n=14)</th>
<th>Postoperative Gabapentin (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>62.3 ± 6.1</td>
<td>62.4 ± 7.2</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>5/9</td>
<td>9/13</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>32.0 ± 7.2</td>
<td>28.9 ± 3.7</td>
</tr>
<tr>
<td>Duration of Surgery (minutes)</td>
<td>68.7 ± 16.8</td>
<td>67.0 ± 17.3</td>
</tr>
</tbody>
</table>

Data are mean ± sd. No significant differences were observed between patients that received postoperative placebo vs. postoperative gabapentin. Consistent with data shown in Table 4.3, mean postoperative pain scores were not different between these two groupings.

Patients that received postoperative gabapentin vs placebo used significantly less PCA morphine at 24 hrs (31 ± 20 mg vs. 52 ± 32 mg), 36 hrs (48 ± 22 mg vs. 77 ± 48 mg) and 48 hrs (57 ± 30 mg vs. 95 ± 57 mg) (all p <0.05) (Figure 4.1).

**Figure 4.1 Cumulative morphine consumption after total knee arthroplasty showing a comparison of patients who received gabapentin postoperatively versus placebo postoperatively.**

Patients who received gabapentin postoperatively used significantly less patient-controlled morphine analgesia (mean ± sd) at 24 hours (31 ± 20 mg versus 52 ± 30 mg), 36 hours (48 ± 22 mg versus 77 ± 48 mg) and 48 hours (57 ± 30 mg versus 95 ± 57 mg) postsurgery. The absence of a difference at 12 hours reflects the ongoing analgesic effect of the peripheral
nerve blocks. All patients received femoral and sciatic nerve blocks with ropivacaine 0.5% (20mL adjacent to each nerve) for postoperative pain (half life 14 ± 3 hours). *p<0.05

Patients that received postoperative gabapentin versus placebo had significantly better active knee flexion on POD 2 (71 ± 12° vs. 59 ± 12°) (p <0.05), POD 3 (80 ± 9° vs. 70 ± 9°) (p <0.05), with a trend toward better flexion on POD 4 (85 ± 9° vs. 78 ± 9°) (p=.08) (Figure 4.2).
Patients who received postoperative gabapentin versus placebo had significantly better active knee flexion on POD 2 (71 ± 12° vs. 59 ± 12°) (p < 0.05), POD 3 (80 ± 9° vs. 70 ± 9°) *(p < 0.05), with a trend toward better flexion on POD 4 (85 ± 9° vs. 78 ± 9°) †(p=.08)

Patients that received gabapentin postoperatively reported significantly less pruritus than patients that received placebo (p<0.05). The two groups did not differ significantly on sedation, nausea, vomiting, or dizziness scores (Table 4.5). There were no reports of post dural puncture headaches and all patients had successful spinal anesthetics.
Table 4.5 Frequency of Adverse Effects over 48 Hours

<table>
<thead>
<tr>
<th>Incidence of:</th>
<th>Postoperative Placebo (N)</th>
<th>Postoperative Gabapentin (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Pruritus*</td>
<td>11*</td>
<td>5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

* Indicates significant difference p<0.05.

4.5 Discussion

The efficacy of gabapentin in reducing opioid consumption has been well documented (Dierking, et al., 2004; Gilron, et al., 2005b; Menigaux, et al., 2005; Pandey, et al., 2005a; Rorarius, et al., 2004; Turan, et al., 2004b; Turan, et al., 2006b; Turan, et al., 2007). Several meta-analyses have demonstrated convincingly that preoperative gabapentin leads to a reduction in postoperative opioid use and reduction in post operative pain scores (Ho, et al., 2006b; Peng, et al., 2007; Seib & Paul, 2006). Furthermore, gabapentin has demonstrated the ability to improve functional recovery after total abdominal hysterectomy (Gilron, et al., 2005b) and anterior cruciate ligament repair (Menigaux, et al., 2005). The results of the present study suggest that perioperative gabapentin when continued for 4 days postoperatively, not only reduces opioid consumption, but also leads to an improvement in active assisted knee flexion. There were no differences in pain scores during this trial. A significant increase in the incidence of pruritus was found in the patients that received postoperative placebo which we attribute to the increased morphine use by these patients.
This interpretation is consistent with the results of a recent study by Sheen and his colleagues showing that patients receiving preoperative gabapentin demonstrated less pruritus following intrathecal morphine injection compared to patients receiving placebo medications (Sheen, Ho, Lee, Tsung, & Chang, 2008).

Gabapentin has been studied extensively in surgical populations that have been given general anesthesia as the primary anesthetic modality. One of the major concerns for health care providers is the incidence of sedation that has been reported in several studies (Gilron, et al., 2005b; Mikkelsen, et al., 2006; Pandey, et al., 2005a; Pandey, et al., 2004a). The postulated main binding site of gabapentin is the \( \alpha_2\delta \) subunit of voltage-dependent calcium channels (Cheng & Chiou, 2006). Recent studies also demonstrate a link to central inhibitory gabaergic pathways in the CNS (Cheng, et al., 2006; Tanabe, Takasu, Takeuchi, & Ono, 2008) and research continues in an effort to elucidate the cellular mechanisms mediating the actions of the gabapentinoids. Given the likelihood of a central depressant mechanism of gabapentin, the interaction of gabapentin and central inhibitory anesthetic agents could be cumulative in the immediate post operative period; thus health care providers often must adjust the dose of intraoperative opioids to avoid excessive sedation when using gabapentin perioperatively. The use of gabapentin with regional anesthesia (spinal/epidural analgesia and peripheral nerve blocks) as the primary surgical modality provides a robust neuronal blockade for hours after surgery. Spinal anesthesia was chosen as the primary anesthetic modality and the peripheral (i.e. femoral and sciatic) nerve blocks were adjuncts for postoperative pain (12 ± 3 hours) (Weber, et al., 2005). Table 4.2 and Figure 4.1 demonstrate the effectiveness of our spinal and peripheral nerve blockade regimen. All patients used very little morphine within the first 12 hours of surgery. Once the peripheral nerve blocks had worn off, the opioid sparing effect of gabapentin became evident. Turan and colleagues found
that gabapentin (1200 mg day) as an adjunct to epidural analgesia decreased pain and analgesic consumption in patients that had undergone lower extremity surgical procedures (Turan, et al., 2006b). In contrast, Adam and colleagues found that a single preoperative dose of 800 mg of gabapentin did not augment postoperative analgesia in patients given interscalene brachial plexus blocks for arthroscopic shoulder surgery (Adam, et al., 2006). It is clear that administration of gabapentin in conjunction with regional anesthesia needs further investigation with respect to timing and the length of administration postoperatively.

Osteoarthritis (OA), the most common reason for TKA, accounts for more difficulty with climbing stairs and walking than any other disease (Felson, et al., 2000; Guccione, et al., 1994). Since one of the primary goals of total knee arthroplasty is to improve physical function, this is an excellent population in which to study the effects of gabapentin on functional outcomes. As stated earlier, many trials have demonstrated an improvement in movement evoked postsurgical pain (Al-Mujadi, et al., 2006; Dirks, et al., 2002; Fassoulaki, et al., 2005b; Gilron, et al., 2005b; Menigaux, et al., 2005; Rorarius, et al., 2004; Turan, et al., 2006b). By including a physical measure (active and passive knee flexion), Menigaux and colleagues demonstrated that gabapentin enhanced mobilization of the knee joint after anterior cruciate ligament repair, thus potentially improving functional recovery (Menigaux, et al., 2005). The results of the present study also show improved physical function in patients that received gabapentin for 4 days after surgery (Figure 4.2) and suggest further research is needed to evaluate the long-term functional outcomes associated with perioperative gabapentin administration.

There are several limitations of the current study. First, the study was significantly underpowered to determine a dose response effect of gabapentin. Several hundred patients
would be needed in order to conduct such a trial. Second, this trial was not double blinded. However, neither the patients nor the physiotherapists involved in the assessment of functional outcomes were aware of the medication or doses that patients received. Finally, there is much debate in the arthroplasty literature as to the value of an isolated physiotherapy measure of function to comprehensively measure outcome (Kennedy, Stratford, Hanna, Wessel, & Gollish, 2006; Terwee, van der Slikke, van Lummel, Benink, Meijers, & de Vet, 2006). Therefore, future research should incorporate a number of functional outcome measures both self report and rehabilitation based to monitor recovery following total knee arthroplasty. Measures such as the 6-minute walk test (Boardman, et al., 2000; Kreibich, et al., 1996), the timed up and go test (Freter & Fruchter, 2000; Ouellet & Moffet, 2002) and a timed stair test (Kennedy, et al., 2002; Walsh, et al., 2001; Walsh, et al., 1998) have all demonstrated reliability and sensitivity to change within the knee arthroplasty population (Kennedy, et al., 2005).
Chapter 5

Study 2

Study 2, presented in Chapter 5 was designed at the same time as the previous chapter. As noted, no trial had been published to date which examined the perioperative dosing of gabapentin during total knee or hip arthroplasty. This randomized, double-blinded study, will compare the effects of a single dose of gabapentin given preoperatively or immediately postoperatively, to placebo, in patients undergoing total hip arthroplasty. This study aims are to demonstrate that 1) gabapentin administration reduces pain and opioid use postoperatively after total hip arthroplasty and 2) preemptive administration of gabapentin is more effective than postoperative administration of gabapentin. Furthermore, we examined the incidence and severity of chronic postsurgical pain 6 months after surgery.

Study 2, Gabapentin Added to a Multimodal Regimen with Spinal Anesthesia does not Reduce Acute Pain, Opioid Consumption or Chronic Pain up to Six Months after Total Hip Arthroplasty was published in Acta Anesthesiologica Scandanvica, Sept 2009; 53 (8):1073-83 and permission to reproduce this manuscript has been obtained from the publisher. This study was also presented at the Annual Meeting of the Canadian Pain Society, Quebec City, Quebec, Canada May 27th – May 30th, 2009.
5 Gabapentin Added to a Multimodal Regimen with Spinal Anesthesia does not Reduce Acute Pain, Opioid Consumption or Chronic Pain up to Six Months after Total Hip Arthroplasty

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Hance A. Clarke, Sara Pereira, Deborah Kennedy, Jeffrey Andrion, Nicholas Mitsakakis, Jeffrey Gollish, Joel Katz, Joseph Kay. Gabapentin added to a multimodal regimen with spinal anesthesia does not reduce acute pain, opioid consumption or chronic pain up to six months after total hip arthroplasty. *Acta Anesthesiologica Scandinavica*, Sept 2009, 53 (8):1073-83.

5.1 Abstract

Background: Gabapentin (GBP) is effective in reducing postoperative pain and opioid consumption, but its effects with regional anesthesia for total hip arthroplasty (THA) are not known. We designed this study to determine whether 1) gabapentin administration reduces pain and opioid use after THA using a multimodal analgesic regimen including spinal anesthesia; 2) preoperative administration of gabapentin is more effective than postoperative administration.

Methods: After REB approval and informed consent, 126 patients were enrolled in a double-blinded, randomized, controlled study. Patients received acetaminophen 1g po, celecoxib 400 mg po, and dexamethasone 8 mg iv, 1-2 hours preoperatively. Patients were randomly assigned to one of three treatment groups (G1: Placebo/Placebo; G2: GBP/Placebo; G3: Placebo/GBP). Patients received gabapentin 600 mg (G2) or placebo (G1 & G3) 2 hours prior to surgery. All patients had spinal anesthesia (15 mg (3cc) of 0.5% hypobaric bupivacaine with 10 micrograms of fentanyl). In the PACU, patients received gabapentin 600 mg (G3) or placebo (G1 & G2). On the ward, patients received acetaminophen 1000 mg po q6h, celecoxib 200 mg po...
q12h, and a morphine PCA device. Patients were interviewed 6 months post surgery to determine the incidence and severity of chronic post-surgical pain.

Results: Mean ± SD cumulative morphine (mg) consumption (G1 = 49.4 ± 24.8, G2 = 47.2 ± 30.1, G3 = 56.1 ± 38.2) at 48 hours and pain scores at 12, 24, 36 and 48 hours post surgery were not significantly different among the groups (G1 (n=38), G2 (n=38), G3 (n=38)). Side effect profiles were similar across groups. Six months after surgery, the number of patients that reported chronic post surgical pain (G1 = 10, G2 = 12, and G3 = 9) and the severity of the pain (G1=4.2 ± 2.9, G2=4.1 ± 2.2, G3=4.9 ± 2.2) did not differ significantly among the groups (p>0.05).

Conclusions: A single 600 mg dose of gabapentin given preoperatively or postoperatively does not reduce morphine consumption or pain scores in hospital or at 6 months after hip arthroplasty within the context of spinal anesthesia and a robust multimodal analgesia regimen.

5.2 Introduction

Total hip arthroplasty is associated with significant pain and decreased mobility in the immediate postoperative period. Moderate to severe postoperative pain is a frequent occurrence after many surgeries (Katz, Jackson, Kavanagh, & Sandler, 1996; Perkins & Kehlet, 2000). Pain of this magnitude has been shown to interfere with postoperative rehabilitation, discharge from hospital and to lead to the development of chronic pain in 3 - 35% of hip arthroplasty patients (Goldstein, et al., 2004). The addition of gabapentin, a non-opioid medication, is effective in reducing, postoperative pain, opioid consumption and
accelerating functional recovery in other types of surgery (Clarke, et al., 2009b; Gilron, et al., 2005b; Menigaux, et al., 2005).

In the clinical setting, post-surgical pain is influenced by at least two factors: the inflammatory response, which is the consequence of trauma to peripheral tissues (i.e., surgical incision, dissection, burns); intra-operative nerve damage arising from nerve transection, crushing, or other nerve injury (Katz & Clarke, 2008; Kelly, et al., 2001; Kissin, 2000). Both factors result in long-term changes in the sensitivity of the central nervous system that amplify the peripheral signal either by excitatory or disinhibitory mechanisms. It is now accepted that while general anesthesia may attenuate transmission of afferent injury barrage from the periphery to the spinal cord and brain, it does not block it (Rundshagen, Kochs, & Schulte am Esch, 1995). Moreover, systemic opioids may not provide a sufficiently dense blockade of spinal nociceptive neurons to prevent central sensitization (Abram & Yaksh, 1993). The processes leading to sensitization of dorsal horn neurons are largely unaffected by general anesthesia or routine doses of opioids. Gabapentin has been extensively studied in general anesthesia paradigms, however few studies have examined its possible preemptive effect when regional anesthesia is used as the primary surgical modality (Adam, et al., 2006; Turan, et al., 2007).

Preventive analgesia has evolved from preemptive analgesia by reducing the importance of blocking solely noxious preoperative stimuli (Katz & Clarke, 2008; J. Katz & C. J. L. McCartney, 2002; Kissin, 1994b). The emphasis is on preventing or obtunding the peripheral nociceptive barrage and central sensitization that arise throughout the entire perioperative period and not simply on blocking preoperative noxious afferent input. A preventive analgesic effect is demonstrated when postoperative pain and/or analgesic consumption is
reduced relative to another intervention, as long as the effect is observed at a point in time that exceeds the clinical duration of action of the target agent. One approach to ascertaining the outer limit of the clinical duration of action of the target agent is to assess pain and analgesic consumption at time points greater than 5.5 half lives of the pharmacologic intervention (Katz, et al., 2011; McCartney, et al., 2004).

In order to facilitate the translation of research into clinical practice, it is important that trials mirror clinical practice. Multimodal analgesia is becoming the standard of practice in most institutions. This practice involves the use of different classes of analgesic agents with different routes of administration to [1] provide superior pain relief at rest and after movement, [2] reduce opioid consumption, and [3] reduce analgesic-related adverse effects (Brown, et al., 2004; Joshi, 2005). Although many clinical trials demonstrate the effectiveness of multimodal analgesia, positive results may not translate into clinical practice (Hsieh & Yealy, 2005; Marshall, 2006). This trial was designed to evaluate the efficacy of gabapentin in the context of a multimodal regimen including preoperative spinal anesthesia (bupivacaine), a COX-2 antagonist (celecoxib), acetaminophen and a steroid (dexamethasone). Although single-agent therapy may attenuate the central nociceptive processing, multimodal therapy is more effective, and may be associated with fewer side effects compared with the high-dose, single-agent therapy (Gilron, et al., 2005a; Moiniche, et al., 1994).

More specifically the novel aspects of this study were to determine whether: 1) a 600 mg dose of gabapentin, added to a robust multimodal analgesia regimen further reduces pain and opioid use after total hip arthroplasty under spinal anesthesia; 2) a 600 mg dose of gabapentin is more effective before versus after surgery (i.e. a preemptive effect); 3) this intervention
leads to any difference in the incidence and severity of chronic pain at 6 months (i.e. a preventive effect).

5.3 Methods

Patient sample and recruitment procedures

The study was approved by the hospital Research Ethics Board and all patients gave informed, written consent to participate. The CONSORT guidelines were followed (i.e. statement for improving the quality of reports of parallel-group randomized trials) with respect to the reporting of this randomized control trial (Moher, Schulz, & Altman, 2001). Patients between the ages of 18-75 with an ASA physical status score of I, II, or III undergoing total hip arthroplasty were eligible for this study. Patients were not eligible if they had a known allergy to any of the medications being used, a history of drug or alcohol abuse, a history of being on chronic pain medications (i.e. slow-release preparations of opioids), rheumatoid arthritis, a psychiatric disorder, a history of diabetes with impaired renal function, a body mass index of greater than 45 or patients unable or unwilling to use patient-controlled analgesia (PCA).

Patients were recruited at their pre-operative assessment visit approximately 1-2 weeks in advance of their surgery. All subjects were screened and the study protocol, the use of the PCA pump, and the visual analogue pain scale (VAS) a 10 cm scale (with endpoints labeled “no pain” and “worst pain possible”) were explained.

Drug preparation, dispensing, and randomization
Gabapentin and placebo medications were encapsulated in identically coloured gelatin capsules and packaged in identical individual blister packs by the Sunnybrook Health Sciences Centre Investigational Pharmacy in order to maintain double-blind conditions. The placebo pills contained a mixture of 50% cellulose and 50% lactose monohydrate. A computer generated randomization schedule was used to assign patients at random in blocks of six to one of the three treatment groups. The schedule was created by the hospital investigational pharmacy which was otherwise not involved in the clinical care of the patients or in the conduct of the trial. The randomization schedule was kept in the pharmacy and none of the investigators had access to it. The pharmacy dispensed the capsules according to the randomization schedule when the investigators informed them that a patient had been recruited into the trial.

*Pre, intra and post-operative Procedures*

On the day of surgery, all patients received acetaminophen 1 g po, celecoxib 400 mg po, and dexamethasone 8 mg iv, 1-2 hours preoperatively. Patients were randomly assigned to one of three treatment groups (G1: Placebo/Placebo; G2: GBP/Placebo; G3: Placebo/GBP). Group 2 received gabapentin 600 mg po 2 hours prior to surgery; the other groups received an identically looking placebo capsule.

All patients were prepared for surgery in a specialized block area. Using an 18 g intravenous cannula, the anesthetist started an intravenous infusion of Lactated Ringer’s solution. Blood pressure, ECG and oximetry monitors were applied. Midazolam 1-3 mg i.v. was administered to achieve anxiolysis. Spinal anesthesia was performed in the lateral decubitus or sitting position. After subcutaneous infiltration with lidocaine 1%, and using a midline approach, a 25 gauge Whitacre needle was inserted at the L3-4, L4-5, or L5-S1 interspace, with the
aperture directed to the side of surgery. When free flow of CSF was obtained, 15 mg of 0.5% hypobaric bupivacaine with 10 micrograms of fentanyl was injected. In all groups, total volume injected to the subarachnoid space was 3.2 mL, with aspiration at the end of injection to ensure that all of the drug was injected intrathecally. The patient was then placed in the lateral decubitus position with the side of surgery uppermost. Patients were then transferred to the operating room where monitors were reapplied, supplemental oxygen was provided, and sedation was administered by an intravenous propofol infusion (25-100 mcg/kg/min) until the end of surgery. The attending anesthesiologist was not involved in the patients’ evaluation postoperatively.

Upon arrival to the recovery room, group 3 received gabapentin 600 mg po; the other groups received an identically looking placebo capsule. At the time of PCA hook up in the PACU (0 hr) and every 4 hours for the next 48 hours, patients were asked to record their pain intensity at rest and after movement using a 10 cm VAS. The PCA pump was set to deliver morphine at 1 mg per demand with a five minute lockout and no background infusion. All patients were instructed to maintain their VAS pain score less than 4/10. If the VAS pain score at rest was 5 cm or greater on two consecutive 4 hourly assessments, the dose of iv PCA morphine was increased to 1.5 mg per demand. At each time point after pain was measured, patients were assessed for the incidence and severity of sedation, nausea, vomiting, and pruritus. On postoperative day 1, movement evoked pain was measured in a standardized manner by asking patients to rate their pain on a visual analogue scale (VAS) after moving from a lying to sitting position at the edge of the bed.

Patients were followed up by telephone 6 months after surgery. A maximum of three calls were made and a voice message was left on the third call. Patients were considered lost to
follow-up if they could not be reached and did not return the call. Patients were administered three questionnaires: A follow-up Hip Arthroplasty Pain questionnaire, The Neuropathic Pain Scale (Galer & Jensen, 1997), and The Hospital Anxiety and Depression Scale (Bjelland, Dahl, Haug, & Neckelmann, 2002). Pain intensity was measured with a numeric rating scale (NRS). The NRS consists of a series of numbers ranging from 0 to 10 with endpoints representing the most extreme pain experiences (0 = no pain and 10 = worst possible pain). The NRS has been shown to have good reliability and validity and is sensitive to change following pharmacological intervention (Katz & Melzack, 1999).

Sample Size Estimate

To determine the number of patients to recruit, data were collected from retrospective chart reviews since we were unable to find a published study examining the effect of gabapentin on pain or morphine consumption in the hip arthroplasty population. After identifying a small subset of charts that resembled the study population (i.e. used a similar anesthetic technique with and without gabapentin), we extracted cumulative PCA morphine consumption. The patients that were given gabapentin prior to surgery (n=10) used 19.06 ± 19.9 mg (mean ± SD) in the first 24 hrs after surgery. The postoperative gabapentin group (n=6) (i.e., administered on arrival in the PACU but not before) used 34.8 ± 13.1 mg (mean ± SD) in the first 24 hrs after surgery. This study was powered to detect a difference between patients that received preoperative gabapentin vs. postoperative gabapentin. Using the means and standard deviations from our chart review, we calculated that 30 subjects per arm (n=90) would provide 95% power at an alpha set at 0.05 to detect a difference of 15.8 mg of morphine consumption between the patients that received gabapentin preoperatively vs. in the postanesthetic care unit.
Statistical Analysis

Data were analyzed with Statistical Analysis Software (SAS for Windows, version 9.1, SAS Institute, Inc, Cary, NC). Demographic data and clinical variables were compared using non-parametric Kruskal-Wallis test for the continuous and Fisher’s exact test for the categorical variables.

Morphine consumption. Morphine consumption, measured at four time points (12, 24, 36 and 48 hrs post surgery) was analyzed by mixed model (PROC MIXED) ANOVA. The model used an autoregressive correlation structure within subjects that decreases with increasing time lag between measures, and an inter-subject random effect of differences between subjects. Group, time and interaction effects were tested with the model. Presence of a significant interaction effect would suggest a difference in the rates of consumption among the three groups.

VAS pain scores. VAS pain scores at rest and after reported movement, measured at 12, 24, 36 and 48 hrs time points were analyzed by mixed model ANOVA as above. The empirical distribution of the scores was investigated visually with the use of histograms and the deviation of the normality assumption of the models was not considered significant.

Postoperative Day (Podsiadlo & Richardson) 1 VAS pain scores while the patient moved from lying to sitting were compared between groups with the use of non-parametric Kruskal-Wallis test.

Adverse effects. Sedation, nausea, vomiting, pruritus and dizziness were assessed across the 48 hour period. Scores were calculated as the proportion of the time points (where a non-missing value was measured) at which the patient experienced the specific adverse effect.
Patients were then classified based on the number of times the specific adverse effect was present: 0%, up to 30% and larger than 30%. The categorizations were compared among the three treatment groups with the use of Fisher’s exact test.

_Six Month Follow-up_

The 6 month pain data were analyzed using the Statistical Package for the Social Sciences (version 16.0 for Windows, SPSS Inc., Chicago, IL, USA). Ordinal variables were compared using the non-parametric Kruskal-Wallis test for independent samples. Categorical variables were analysed using the Fisher’s exact test.

### 5.4 Results

_Recruitment and Retention of Patients_

Overall 439 patients were screened for recruitment into the trial between May 2006 and April 2008. Of these, 121 did not meet the inclusion criteria (34 were older than 75 years of age, 29 had diabetes and/or an elevated creatinine, 16 declared an allergy to one of the study medications, 12 had a history of being on chronic pain medications, 11 presented with a psychiatric disorder, 9 had a BMI > 45, 5 were not proficient in English, and 5 had Rheumatoid Arthritis). Of the 318 patients that were eligible to participate, 126 patients were randomized to one of the three study groups. 114 patients completed the in-hospital protocol. Reasons for not completing the in hospital protocol were cancellation of surgery after taking the preoperative medications (n=4), patients that requested withdrawal from the study (n=2), patients that received general anesthesia (n=2), failure of the spinal anesthetic (n=1), surgeon withdrawal of patient (n=1) one patient that had a more extensive surgical procedure
performed (n=1).

Six months after surgery, 82 (71.9%; 51 male, 31 female) patients were followed up. Between the in-hospital intervention and 6 month follow-up, 20 patients were lost to follow up (unable to be contacted) and 12 refused to be interviewed. Of the 82 patients that were followed up, 28, 28, and 26 patients were in Groups 1, 2, and 3 respectively.

Demographic and Clinical Variables

Table 5.1 shows the demographic and clinical variables describing the sample of 117 patients. The groups were comparable with respect to age, gender, body mass index, ASA status and duration of surgery.

Table 5.1 Demographic Characteristics and Duration of Surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>(G1) Placebo/Placebo (n=39)</th>
<th>(G2) GBP 600/Placebo (n=40)</th>
<th>(G3) Placebo/GBP 600 (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61.3 ± 10.7</td>
<td>58.9 ± 9.4</td>
<td>60.4 ± 8.1</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>21 / 18</td>
<td>27 / 11</td>
<td>22 / 16</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>29.2 ± 5.3</td>
<td>29.2 ± 5.4</td>
<td>29.0 ± 6.3</td>
</tr>
<tr>
<td>ASA (I/II/III)</td>
<td>5 / 28 / 6</td>
<td>6 / 28 / 6</td>
<td>7 / 26 / 5</td>
</tr>
<tr>
<td>Duration of Surgery (minutes)</td>
<td>73.8 ± 22.7</td>
<td>76.0 ± 19.8</td>
<td>70.9 ± 15.0</td>
</tr>
</tbody>
</table>

Data are mean ± SD. No significant differences were observed among groups.

In-Hospital Intervention

Overall, significant differences among the three groups (G1 = Placebo, G2= Preemptive
GBP, G3 = Postop. GBP) were not found (p=0.53) in morphine consumption over the first 48 postoperative hours (Figure 5.1). The group x time interaction effect (measuring possible differences in rates of consumption) was not significant (p=0.09).

![Figure 5.1 Cumulative morphine consumption after total hip arthroplasty.](image)

Likewise, pain scores did not differ significantly at rest (p=0.49) or with movement (p=0.91) over the first 48 hours (Figure 5.2). The group x time interaction was not significant for rest or movement pain scores (p=0.94 and 0.11, respectively).
Figure 5.2 Pain Scores at rest and with movement after total hip arthroplasty

On postoperative day 1, there was no difference in pain scores upon moving from lying to the sitting position at the edge of the bed (G1 = 39.4 ± 25.8, G2 = 40.3 ± 22.0, G3 = 38.7 ± 24.5) (mean ± SD) (p=0.89). Finally, the three groups did not differ significantly with respect to sedation (p=0.51), nausea (p=0.95), vomiting (p=0.2), pruritus (p=0.79) or dizziness (p=0.84) (Table 5.2).

Table 5.2 Side Effect Profiles

<table>
<thead>
<tr>
<th>Percent of time patient experienced:</th>
<th>(G1) Placebo/Placebo (n=38)</th>
<th>(G2) GPN 600/Placebo (n=38)</th>
<th>(G3) Placebo/GPN 600 (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEDATION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>0% Sedation</td>
<td>31</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>&lt;30% Sedation</td>
<td>7</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>&gt;30% Sedation</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NAUSEA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0% Nausea</td>
<td>24</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>&lt;30% Nausea</td>
<td>13</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>&gt;30% Nausea</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PRURITUS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0% Pruritus</td>
<td>28</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>&lt;30% Pruritus</td>
<td>8</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>&gt;30% Pruritus</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>DIZZINESS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0% Dizziness</td>
<td>30</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>&lt;30% Dizziness</td>
<td>8</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>&gt;30% Dizziness</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>VOMITING</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0% Vomiting</td>
<td>31</td>
<td>31</td>
<td>36</td>
</tr>
<tr>
<td>&lt;30% Vomiting</td>
<td>7</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

* Indicates significant difference p<0.05.

**Six Month Chronic Pain Follow-up**

Six months following total hip arthroplasty surgery, neither the incidence of chronic post surgical pain, nor anxiety or depression scores differed significantly among the groups (all p>.05). Of the 82 patients that were interviewed at 6 months, 31 (37.8%) patients reported chronic pain related to their hip arthroplasty (i.e. 27% of the entire study cohort). The characteristics/severity of the pain described by the 31 patients that reported pain (G1 = 10, G2 = 12, and G3 = 9) are shown in Table 5.3. Average pain scores reported at 6 months were
< 4/10 and appeared to have minimal impact on daily functioning. Pain scores at “the worst” were in the moderate range (G1= 4.2 ± 2.9, G2= 4.1 ± 2.2, G3= 4.9 ± 2.2) (p=0.61).

Table 5.3 Six month Pain Profile (Patients with chronic pain only)

<table>
<thead>
<tr>
<th>Total Hip Arthroplasty Follow up Pain Questionnaire</th>
<th>(G1) Placebo/Placebo (n=10 of 28 patients reported chronic post surgical pain)</th>
<th>(G2) GPN 600/Placebo (n=12 of 28 patients reported chronic post surgical pain)</th>
<th>(G3) Placebo/GPN 600 (n=9 of 26 patients reported chronic post surgical pain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often do you have Pain at your arthroplasty site?</td>
<td>Constant: 2 Periodic: 5 Brief: 3</td>
<td>Constant: 4 Periodic: 5 Brief: 3</td>
<td>Constant: 1 Periodic: 4 Brief: 4</td>
</tr>
<tr>
<td>Measurement of Allodynia: Number of patients who reported that running their finger along their scar is painful.</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Measurement of Hyperalgesia: Number of patients who reported that lifting their knee to 90° hurt or felt uncomfortable.</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Usual intensity of your post hip arthroplasty site pain (0 – 10)</td>
<td>3.4 ± 1.6</td>
<td>3.1 ± 1.9</td>
<td>3.1 ± 1.5</td>
</tr>
<tr>
<td>The worst intensity of your post hip arthroplasty site pain (0 – 10)</td>
<td>5.6 ± 3.1</td>
<td>4.6 ± 1.9</td>
<td>5.3 ± 2.1</td>
</tr>
<tr>
<td>The extent to which your post hip arthroplasty site pain interferes with your everyday activities (0 – 10)</td>
<td>3.9 ± 3.3</td>
<td>3.6 ± 3.6</td>
<td>4.1 ± 3.6</td>
</tr>
<tr>
<td>Neuropathic Pain Scale Items</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q.1 how intense is your pain.</td>
<td>3.6 ± 1.9</td>
<td>2.9 ± 1.7</td>
<td>3.9 ± 2.6</td>
</tr>
<tr>
<td>Q.2 how sharp your pain feels</td>
<td>2.2 ± 2.3</td>
<td>2.1 ± 2.7</td>
<td>2.4 ± 1.9</td>
</tr>
<tr>
<td>Q.3 how hot your pain feels.</td>
<td>0.9 ± 1.9</td>
<td>0.2 ± 0.4</td>
<td>0.6 ± 1.1</td>
</tr>
<tr>
<td>Q.4 how dull your pain feels.</td>
<td>3.3 ± 2.9</td>
<td>2.0 ± 2.5</td>
<td>3.0 ± 2.2</td>
</tr>
<tr>
<td>Question</td>
<td>Description</td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Q.5</td>
<td>How cold your pain feels.</td>
<td>0.3 ± 0.9</td>
<td>1.0 ± 2.0</td>
</tr>
<tr>
<td>Q.6</td>
<td>How sensitive your skin is to light touch or clothing.</td>
<td>1.6 ± 2.8</td>
<td>0.5 ± 1.0</td>
</tr>
<tr>
<td>Q.7</td>
<td>How itchy your pain feels.</td>
<td>0.0 ± 0.0</td>
<td>0.8 ± 1.6</td>
</tr>
<tr>
<td>Q.8</td>
<td>How unpleasant your pain feels.</td>
<td>3.7 ± 2.6</td>
<td>3.7 ± 2.7</td>
</tr>
<tr>
<td>Q10a</td>
<td>How unpleasant is your deep pain.</td>
<td>4.0 ± 2.8</td>
<td>2.9 ± 2.4</td>
</tr>
<tr>
<td>Q10b</td>
<td>How unpleasant is your superficial pain</td>
<td>1.4 ± 1.4</td>
<td>0.9 ± 1.0</td>
</tr>
</tbody>
</table>

**Hospital Anxiety and Depression Scores**

<table>
<thead>
<tr>
<th>Score</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>5.8 ± 3.0</td>
<td>5.1 ± 2.6</td>
<td>3.0 ± 2.3</td>
</tr>
<tr>
<td>Depression</td>
<td>4.0 ± 3.0</td>
<td>3.1 ± 2.9</td>
<td>5.1 ± 5.4</td>
</tr>
</tbody>
</table>

Data are mean ± SD. No significant differences were observed among groups. PACU = Post Anesthetic Care Unit

### 5.5 Discussion

Gabapentin has been efficacious in reducing opioid consumption after many types of surgery (Dierking, et al., 2004; Gilron, et al., 2005b; Menigaux, et al., 2005; Pandey, et al., 2005a; Rorarius, et al., 2004; Turan, et al., 2004b; Turan, et al., 2006b). Meta-analyses have demonstrated this anticonvulsant leads to a reduction in postoperative opioid use and a reduction in postoperative pain scores (Ho, et al., 2006b; Peng, et al., 2007; Seib & Paul, 2006). The results of the present study demonstrate that a 600 mg dose of gabapentin whether administered preoperatively or postoperatively, in the context of a robust multimodal analgesia regimen with spinal anesthesia, does not reduce postoperative opioid consumption or pain scores (Figures 5.1 and 5.2). Given the recent increase in use of gabapentin within the perioperative setting, this novel work examines the potential added benefit of a single preemptive dose to an already clinically robust pain regimen. When compared to the current gabapentin literature, this trial has a larger sample size than most studies published thus far.
Therefore, our results question the addition of a single dose of gabapentin to an already satisfactory clinical regimen. However, gabapentin continued into the postoperative period has been found to be beneficial for movement evoked pain in other patient populations (Gilron, et al., 2005b; Menigaux, et al., 2005) and may also be beneficial with respect to post arthroplasty rehabilitation. The potential benefit of the gabapentinoids on improving inpatient rehabilitation throughout the perioperative stay is currently under investigation and a recent publication has shown promising results with improvement in active assisted knee flexion after total knee arthroplasty (Clarke, et al., 2009b). Recent studies looking at gabapentin in association with regional anesthesia techniques have yielded mixed results. A recent study by Turan and colleagues (Turan, et al., 2006b) showed, that gabapentin (1200 mg day) as an adjunct to epidural analgesia decreased pain and analgesic consumption in patients that had undergone lower extremity surgical procedures. In a second study by the same group (Turan, et al., 2007), the same dose of gabapentin administered preoperatively decreased tourniquet-related pain and improved the quality of anesthesia during hand surgery under intravenous regional anesthesia (IVRA). In contrast, Adam and colleagues (Adam, et al., 2006) found that a single preoperative dose of 800 mg of gabapentin did not augment postoperative analgesia in patients given interscalene brachial plexus blocks for arthroscopic shoulder surgery. Similarly, Brogly and colleagues recently demonstrated that patients undergoing thyroidectomy and receiving a single preemptive dose of 1200 mg of gabapentin within the context of cervical plexus blocks did not have a reduction in acute pain or opioid consumption (Brogly, et al., 2008). However a single 1200 mg dose of gabapentin did prevent delayed neuropathic pain at six months compared to the patients that received placebo (Brogly, et al., 2008). It is clear that gabapentin in conjunction with regional
anesthesia regimens needs further investigation with respect to timing and the duration of administration postoperatively.

The results of the present study indicate that the rationale for using a single preoperative dose of gabapentin in the context of regional anesthesia should be questioned. Unless gabapentin significantly modifies central sensitization in the long term, the addition of a single preoperative dose in conjunction with regional blocks seems somewhat redundant. Given the ability of local anesthetics to completely block pain and decrease morphine consumption in the acute postsurgical time period, the addition of a single preoperative dose will likely not further reduce pain or opioid consumption as demonstrated by our results and others (Adam, et al., 2006; Brogly, et al., 2008). However starting gabapentin preoperatively and continuing this medication into the postoperative time period could lead to an opioid sparing effect and may reduce pain with functional recovery and rehabilitation (Clarke, et al., 2009b; Gilron, et al., 2005b). Gabapentin has been investigated as an adjunct to rehabilitation due to its efficacy in reducing movement evoked pain (Al-Mujadi, et al., 2006; Clarke, et al., 2009b; Fassoulaki, et al., 2005b; Gilron, et al., 2005b; Menigaux, et al., 2005; Rorarius, et al., 2004).

Pandey et al. (Pandey, et al., 2005a) randomized patients undergoing lumbar discectomy to receive a one time dose of either, placebo or gabapentin 300 mg, 600 mg, 900 mg, or 1200 mg preoperatively. The optimal dose was 600 mg; at higher doses (900 and 1200 mg) patients exhibited more side effects with no additional reduction in pain. At our institution, patients that received greater than 600 mg of gabapentin prior to surgery as part of daily clinical practice demonstrated an increased incidence of sedation. Using a design similar to that of the present study, and using the same patient population, Mathiesen and colleagues randomized 120 patients to either (A) placebo, (B) pregabalin 300 mg, or (C) pregabalin 300
mg and dexamethasone 8 mg prior to total hip arthroplasty (Mathiesen, et al., 2008). All patients also received acetaminophen 1 g and a standardized spinal anaesthetic prior to surgery. After 24 hours, morphine consumption was significantly reduced in groups B and C compared with Group A. There are differences between the present study and that of Mathiesen et al. First, the bioequivalent dose of 300 mg pregabalin is approximately 1800 mg of gabapentin (6:1) which would be three times the dose used in our trial (which also demonstrated increased sedation). Second, Mathiesen et al did not use a COX-2 antagonist as part of their pain regimen. It is clear that more work needs to be done with regard to the optimal dosing of gabapentin in various surgical populations and the determination of the efficacy at treating postoperative pain beyond the immediate 24 or 48 hours of surgery.

Most trials thus far have compared gabapentin to placebo. Gilron (Gilron, et al., 2005b) and Turan (Turan, et al., 2006b) published studies in which they administered gabapentin and Cox II inhibitors, and compared to each agent in isolation. Both studies demonstrated a superior opioid sparing and pain reducing effect in patients that received the multimodal intervention. Our multimodal regimen involved spinal anesthesia (bupivacaine), a COX-2 antagonist (celecoxib), acetaminophen and a steroid (dexamethasone). By using the above multimodal regimen, we likely established an effective level of preemptive analgesia before the surgical injury, and then continued the effective analgesic level well into the post-injury period to prevent central sensitization during the immediate postoperative time period. The pain scores throughout our trial were excellent (figure 5.2). Regardless of the intervention (gabapentin administration before or after surgery or placebo), patients reported pain scores in the mild range (< 4/10) both at rest, with movement, and while moving from lying to sitting on POD1. It is clear that the single dose of gabapentin had no effect on an already robust perioperative pain regimen.
Six months following total hip arthroplasty surgery, the incidence of chronic post surgical pain, anxiety and depression scores were similar across groups. Of the 82 patients that were reached via telephone interview 31 patients (37.8%) reported chronic pain related to their hip arthroplasty. It has been suggested that the severity of acute pain may be related to the development of chronic pain (Brander, Stulberg, Adams, Harden, Bruehl, Stanos, & Houle, 2003; Katz, et al., 1996; Thomas, Robinson, Champion, McKell, & Pell, 1998). Other mechanisms underlying the transition to chronicity may involve ectopic neural activity (Pitcher & Henry, 2008), psychological factors (Katz, Gordon, McCrae, & Halket, 2009) and genomics (Edwards, 2006). Forty percent (40%) of the patients in the present study reported post surgical pain at 6 months notwithstanding the mild acute pain intensity experienced in the days after surgery. At the 6 month interview, the usual intensity of the pain was less than 4/10 across all groups and the pain did not interfere significantly with their daily activities. It is important to note that this study was powered for acute pain outcomes, even though we were able to contact 71% of patients postoperatively, the possibility remains that this study may be underpowered to detect group differences with respect to the intensity of chronic post surgical pain. The incidence of chronic post surgical pain at 6 months (37.8%) may be an over-estimate of the true incidence since it is possible that mainly patients with chronic pain agreed to be followed up. Using the entire cohort as the denominator yielded a lower estimate (27%) of the incidence which remains higher than expected.

There are several limitations of this study. First, the optimal dose of preemptive gabapentin has not been elucidated in hip arthroplasty patients. It is unlikely that giving even higher doses of this anticonvulsant in the context of regional anesthesia would change the observed outcome in the context of regional anesthesia techniques (spinal blockade, peripheral blocks, etc.) because the half life of a single dose of gabapentin (i.e. 6-8 hours) often does not outlast
the effective times of the regional anesthetic. The present results are specific to our multimodal analgesic design and cannot be generalized to the same surgery and other surgeries performed under general anesthesia. Second, even though the incidence of chronic pain seen in this study is higher than reported elsewhere in the literature (Goldstein, et al., 2004), the severity and impact on patient functioning appears to be minor (Table 3). Another limitation is that we did not assess the incidence or intensity of pain prior to surgery. Given that the majority of patients undergoing THA have significant levels of pain and disability before surgery (Cremeans-Smith, et al., 2009), it is quite possible that the 37.8% (who reported mild pain 6 months after surgery) represents an improvement relative to their preoperative pain and functioning. Future studies examining the course of pain over time should collect baseline preoperative data.

In conclusion, a single 600 mg dose of gabapentin whether given preoperatively or postoperatively did not reduce morphine consumption or pain scores in hospital or at 6 months post hip arthroplasty. Gabapentin administration, in conjunction with regional anesthesia and multimodal regimens, requires further investigation with respect to timing and the duration of administration postoperatively.
Chapter 6

Study 3

To date, there had been two published studies regarding the effectiveness of gabapentin for pre-operative anxiolysis. Given the mixed results (described in Section 6.2), we tested a secondary research question in order to determine whether 600 mg of gabapentin reduced preoperative anxiety. Using novel data collected within the previous double blinded randomized placebo controlled trial (Study 2) we examined whether the preoperative administration of 600 mg of gabapentin versus an identical placebo capsule decreased preoperative anxiety in patients scheduled for total hip arthroplasty under spinal anesthesia.

Study 3, Gabapentin does not Reduce Preoperative Anxiety when Given Prior to Total Hip Arthroplasty was published in Pain Medicine, June 2010, 11 (6):966-71, and permission to reproduce this manuscript has been obtained from the publisher. I’d like to thank statistician Nicholas Mitsakakis for his input with the current chapter.
6 Gabapentin does not Reduce Preoperative Anxiety when Given Prior to Total Hip Arthroplasty

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6.1 Abstract

Introduction: Gabapentin is an antiepileptic drug which is also used for the treatment of postoperative pain and a variety of psychiatric diseases including chronic anxiety disorders. We tested the hypothesis that compared with a placebo control, gabapentin would reduce preoperative anxiety in patients undergoing total hip arthroplasty.

Methods: Following ethics approval, patients participating in a larger double blind, randomized, trial of multimodal analgesia were given either gabapentin 600 mg (n = 22) or placebo (n = 48) two hours before spinal anesthesia. Prior to administering the study medication, baseline anxiety levels were measured using a visual analogue scale (VAS). Two hours after the ingestion of gabapentin or placebo, and prior to surgery, patients again rated their anxiety using a VAS.

Results: Anxiety scores did not differ significantly between the groups either before (p = 0.95) or two hours after (p = 0.61) ingestion of gabapentin or placebo. Baseline anxiety and post-drug anxiety scores failed to demonstrate a significant association with maximal postoperative pain at rest, maximal postoperative pain with movement, and cumulative morphine consumption 48hrs after surgery.
Conclusions: Administration of gabapentin 600 mg prior to surgery does not reduce preoperative anxiety.

6.2 Introduction
Gabapentin, a structural analogue of \( \gamma \)-aminobutyric acid, was initially used as an anticonvulsant and antinociceptive drug (Cheng & Chiou, 2006). Its exact mechanism of action is unknown but gabapentin is thought to bind to the \( \alpha_{2\delta} \) subunit of voltage-dependent calcium channels (Taylor, 2009). More recently, gabapentin has been used extensively for the treatment of acute postsurgical pain, in part due to a mild adverse-effect profile which includes (% patients): somnolence (20%), dizziness (18%), ataxia (13%), and fatigue (11%) (Rose & Kam, 2002). Gabapentin has been found to be an effective perioperative analgesic following abdominal or pelvic surgery (Gilron, et al., 2005b; Rorarius, et al., 2004; Turan, et al., 2006b), musculoskeletal surgery (Clarke, et al., 2009b; Pandey, et al., 2005a; Turan, et al., 2004a), head and neck surgery (Al-Mujadi, et al., 2006; Mikkelsen, et al., 2006), breast surgery (Dirks, et al., 2002; A. Fassoulaki, et al., 2002b; Fassoulaki, et al., 2005b), varicocele surgery (Koc, et al., 2007) and thoracic surgery (Huot, et al., 2008). Several meta-analyses have confirmed the efficacy of gabapentin in reducing postoperative opioid use and pain scores (Ho, et al., 2006b; Peng, et al., 2007; Seib & Paul, 2006). Gabapentin has also been found to be efficacious in the treatment of various psychiatric disorders such as social anxiety disorder (Pande, et al., 1999), bipolar disorder (Vieta, et al., 2006) and post traumatic stress disorder (Brannon, et al., 2000; Malek-Ahmadi, 2003). In recent years, gabapentin has become a frontline drug in the treatment of chemical addiction (Verduin, McKay, & Brady, 2007) as evidenced by its ability to diminish addiction seeking behaviours (Clemens & Vendruscolo, 2008).
The efficacy of using gabapentin for the treatment of pre-operative anxiety in patients who are unable to tolerate benzodiazepines deserves further study. A recent study demonstrated that preoperative anxiety was significantly lower in patients given gabapentin versus placebo prior to anterior cruciate ligament repair (Menigaux, et al., 2005). However, pre-drug, baseline anxiety scores were not measured raising concern about the veracity of the observation. In another study, gabapentin was less effective in reducing pre-operative anxiety when compared to an active placebo (15 mg of oxazepam) in patients undergoing vaginal hysterectomy (Rorarius, et al., 2004). However, these authors also did not report pre-drug baseline anxiety scores. In a recent study by White and colleagues, pregabalin (75–300 mg po), a newer α2δ subunit voltage-dependent calcium channel blocker, increased perioperative sedation in a dose-related fashion, but failed to reduce preoperative state anxiety when given preoperatively (White, Tufanogullari, Taylor, & Klein, 2009a). Using a dental anxiety model, 150 mg of pregabalin recently demonstrated good anxiolytic efficacy when compared to controls, however patients experienced increased somnolence (Nutt, Mandel, & Baldinetti, 2009).

Given the mixed results, we tested the hypothesis that gabapentin reduces preoperative anxiety. Using novel data collected within a double blinded randomized placebo controlled trial (Clarke, et al., 2009a) we examined whether the preoperative administration of 600 mg of gabapentin versus an identical placebo capsule decreased preoperative anxiety in patients scheduled for total hip arthroplasty under spinal anesthesia. The design of the original trial consisted of three treatment groups: Group 1 (placebo/placebo); Group 2 (gabapentin 600mg/placebo); Group 3: (placebo/gabapentin 600mg) (i.e. treatment received 2 hours prior to surgery/ treatment received in the post operative anesthetic care area) (Clarke, et al., 2009a). Only Group 2 received gabapentin 2 hours prior to surgery, therefore anxiety data
from groups 1 and 3 were combined for the placebo group.

### 6.3 Methods

This study was approved by the Research Ethics Board of the Sunnybrook Health Sciences Centre and all patients gave informed, written consent to participate. Patient’s between the ages of 18-75 with an ASA physical status score of I, II, or III undergoing total hip arthroplasty were eligible for this study. Patients were not eligible if they had a known allergy to any of the medications being used, a history of drug or alcohol abuse, a history of being on chronic pain medications (i.e. slow-release preparations of opioids), rheumatoid arthritis, a psychiatric disorder, a history of diabetes with impaired renal function, a body mass index of greater than 45 or patients unable or unwilling to use patient-controlled analgesia (PCA). Patients were identified and recruited at their pre-operative anesthesia assessment visit approximately 1-2 weeks in advance of their surgery. All subjects were screened and the study protocol, along with the use of the visual analogue anxiety scale (VAS) a 100 mm scale (with endpoints labeled “No anxiety” and “Extreme Anxiety”) were explained at the time of enrollment.

The present sample comprised 70 patients who participated in a double blind, randomized, controlled trial in which all patients received acetaminophen 1g po, and celecoxib 400 mg po 2 hours preoperatively (Clarke, et al., 2009a). The primary foci of the study were the effects of gabapentin (GBP) on anxiety, postoperative pain and opioid consumption. Patients were randomly assigned to one of three treatment groups (before/after anesthesia): Group 1: Placebo/Placebo (n=24); Group 2: GBP/Placebo (n=22); Group 3: Placebo/GBP (n=24). Group 2 received gabapentin 600 mg po 2 hours prior to surgery; the other groups received an identically looking placebo capsule. Prior to the administration of the preoperative
medications in the presurgical waiting area, all patients were asked to rate their baseline anxiety level prior to surgery on a 100 mm visual analogue scale. This Visual Analogue Scale was similar to the scale used by Menigaux and colleagues (Menigaux, et al., 2005). Upon arrival to the regional anesthesia care area (two hours after the ingestion of gabapentin or placebo), patients were asked by a nurse to again rate their current level of anxiety using an identical 100 mm visual analogue scale.

**Statistical Power**

The present study has sufficient power for the detection of an effect equivalent to a 20% reduction in baseline anxiety scores in the treatment group when compared to controls. Given our sample size (n=48 for the controls and n=22 for the treatment group) and under the assumption that the coefficient of variation of the control group is equal to 0.3, the current study has 96.3% power to detect a significant decrease in baseline anxiety. The above assumptions are based on the results found in the Menigaux study. That study had a total of 40 patients (N=20 patients per group) and demonstrated that preoperative VAS anxiety scores were significantly lower in the gabapentin group than in the control group (28 ± 16 versus 66 ± 15 mm, respectively; P  0.0001) (Menigaux, et al., 2005).

**Statistical Analysis**

Age, gender, body mass index and ASA status, as well as baseline and pre-operative anxiety scores were compared between patients who received gabapentin (Group 2, n = 22) or placebo (Groups 1 and 3, n = 48), using the non-parametric Wilcoxon test (for continuous data) and Fisher’s Exact test (for categorical data). A non-parametric test was used for the continuous variables because their distributions deviated from the normal.
To reduce any bias in post-drug anxiety scores introduced by potential differences in the baseline (pre-drug) anxiety scores, an analysis of covariance (ANCOVA) model was fitted, using the baseline (pre-drug) anxiety scores as the covariate (Snedecor, 1956). The ANCOVA model used the post-drug ingestion anxiety score as a continuous outcome, the treatment group as a factor and the baseline anxiety score as a continuous covariate. The model tested whether gabapentin administration had any effect on the post-drug anxiety scores after adjusting for the variance in baseline anxiety scores.

Anxiety: Postoperative Pain and Opioid Consumption

The non-parametric Spearman's rank correlation was used to test for an association between anxiety (baseline or preoperative) and the following postoperative variables; maximal pain at rest, maximal pain with movement, and cumulative morphine consumption at 48hrs.

6.4 Results

The two groups were comparable with respect to age, gender, BMI, ASA status, pre-drug baseline anxiety scores, and post-drug anxiety scores (Table 6.1).

Table 6.1 Medians (frequencies) and inter quartile ranges (percentages) for continuous (categorical) variables. Wilcoxon (Fisher’s Exact) test p-values are also reported.

<table>
<thead>
<tr>
<th></th>
<th>Gabapentin (n = 22)</th>
<th>Placebo (n = 48)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59 (53-69)</td>
<td>63.5 (55.5-68.5)</td>
<td>0.35</td>
</tr>
<tr>
<td>Gender (M)</td>
<td>13 (56.5)</td>
<td>26 (54.2)</td>
<td>1</td>
</tr>
<tr>
<td>BMI</td>
<td>28.5 (24.9-31.1)</td>
<td>29.3 (25.1-33.9)</td>
<td>0.55</td>
</tr>
<tr>
<td>ASA = 1</td>
<td>3 (13.0)</td>
<td>4 (8.3)</td>
<td></td>
</tr>
<tr>
<td>ASA = 2</td>
<td>15 (65.2)</td>
<td>35 (72.9)</td>
<td>0.78</td>
</tr>
</tbody>
</table>
A significant difference was not found in post-drug anxiety scores between gabapentin- and placebo-treated patients after adjusting for baseline anxiety scores (Table 6.2).

Table 6.2 Analysis of covariance model results comparing preoperative anxiety scores in gabapentin vs placebo treated patients.

| Parameter                        | Estimate | Standard Error | t Value | Pr > |t| |
|----------------------------------|----------|----------------|---------|------|---|
| Intercept                        | 7.52     | 2.45           | 3.06    | 0.0031 |
| Group                            | 3.99     | 2.62           | 1.52    | 0.1320 |
| Baseline anxiety                 | 0.84     | 0.05           | 15.93   | <.0001 |

Significant between group differences in preoperative anxiety scores were not observed after controlling for baseline anxiety levels.
Theses results demonstrate that anxiety scores were not different after treatment with gabapentin or placebo, regardless of patients’ baseline level of anxiety. Table 3 shows the correlation coefficients between anxiety scores (pre-drug and post-drug) and acute postoperative endpoints. Baseline pre-drug anxiety and post-drug anxiety failed to demonstrate a significant association with any of the postoperative variables; maximal pain at rest, maximal pain with movement, and cumulative morphine consumption 48hrs after surgery (Table 6.3).

**Table 6.3** Spearman rank correlations demonstrating no significant associations with baseline pre-drug anxiety or post-drug anxiety and cumulative morphine consumption, maximal pain at rest, or maximal pain with movement.

<table>
<thead>
<tr>
<th></th>
<th>Baseline anxiety</th>
<th>Post-drug anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation</td>
<td>P – Value</td>
</tr>
<tr>
<td>Cumulative morphine consumption at 48 hours</td>
<td>-0.08</td>
<td>0.49</td>
</tr>
<tr>
<td>Maximal pain at rest</td>
<td>0.12</td>
<td>0.28</td>
</tr>
<tr>
<td>Maximal pain with movement</td>
<td>0.11</td>
<td>0.38</td>
</tr>
</tbody>
</table>

**6.5 Discussion**

These results indicate that gabapentin 600 mg did not produce anxiolysis compared with placebo when administered two hours prior to total hip arthroplasty. These results contrast with those of a previous study in which preoperative anxiety scores were reported to be lower
in patients who received gabapentin 1200 mg (Menigaux, et al., 2005) and are congruent with the results by White and colleagues with respect to pregabalin and preoperative anxiety (White, et al., 2009a). However, unlike in the present study, Menigaux et al. did not obtain a baseline (pre-drug) measure of anxiety prior to the administration of gabapentin, raising the possibility that the observed differences in anxiety reported after gabapentin reflect pre-existing baseline differences that went undetected. The same criticism can be made of the Rorarius trial which reported that active placebo (i.e. patients receiving oxazepam 15 mg) were less anxious than those in the gabapentin group (1200 mg) upon arrival to the operating room theatre (Rorarius, et al., 2004). Once again, there was a lack of baseline anxiety data.

Many of the perioperative trials reported thus far, suggest that a single dose of 1200 mg of gabapentin orally administered prior to surgery is safe and has only minor side effects (Dirks, et al., 2002; Turan, et al., 2004a; Turan, et al., 2004c). However, a body of evidence has emerged which points to the need for added vigilance when using gabapentin in the elderly and in patients with significantly compromised renal function (Attupurath, Aziz, Wollman, Muralee, & Tampi, 2009; Dogukan, Aygen, Berilgen, Dag, Bektas, & Gunal, 2006; Hung, Seow, Chong, Wang, & Chen, 2008; Miller & Price, 2009; Peterson, 2009). It is possible that the gabapentin dose used in our trial was too low to demonstrate a significant anxiolytic effect. The rationale for choosing the 600 mg dose of gabapentin was the following: [1] gabapentin administration at doses greater than 600 mg preoperatively have demonstrated increased side effects such as dizziness, sedation, and ataxia without any further benefit with respect to analgesia (Pandey, et al., 2005a), [2] preoperative administration of 600 mg of gabapentin is routinely used for multimodal perioperative regimens, in which regional anesthesia is used as the main anesthetic modality, for lower limb arthroplasty (Clarke, et al., 2009a; Clarke, et al., 2009b), and [3] patients undergoing
total joint arthroplasty are significantly older than previously studied cohorts which increases patient vulnerability to the side effects of gabapentin. Given that early rehabilitation is one of the most important endpoints after total joint arthroplasty, the prevention of side effects that might have impaired patient physical functioning on postoperative day 1 was a major factor in the choice of adding the 600mg of gabapentin to our perioperative pain regimen. Finally, sedation, drowsiness and dizziness that tend to occur at the higher initial drug doses may well have confounded the assessment of anxiolysis (Gilron, et al., 2005b; Nutt, et al., 2009; Pandey, et al., 2005a; Turan, et al., 2006b). Differences were not observed with respect to sedation, dizziness, and ataxia between the two groups at any point in this trial (Clarke, et al., 2009a).

Although advances in anesthesia and surgical techniques continue to evolve at a rapid rate, the treatment of adult preoperative anxiety has remained relatively constant over the past decade. Benzodiazepines remain the drug of choice for the treatment of preoperative anxiety. Alternative treatments should continue to be investigated for the subset of patients that may be unable to tolerate this medication (i.e. an allergic response or recovering from physical dependence/addiction to the medication). A head to head comparison with respect to benzodiazepines is warranted. Further well-controlled and well designed studies are needed before gabapentin can be recommended for the “off-label” treatment of preoperative anxiety.
Chapter 7

Study 4

Given the negative finding in Study 3 (Chapter 6) and the shortcomings in the studies which examined the anxiolytic properties of gabapentin to date, such as the low baseline anxiety levels observed, the lack of pre-drug baseline anxiety scores or the inclusion of an appropriate placebo control group (Section 7.2) study 4 was designed. The randomized, placebo-controlled, double-blind trial presented in chapter 7 provides a methodological improvement on previous work performed in the area of gabapentin and preoperative anxiolysis. Frist, we measured anxiety prior to drug administration to ensure that any post-drug differences were not due to pre-existing levels of anxiety. Second, we selected a patient population that exhibited moderate to high levels of preoperative anxiety; previous trials have not screened patients for preoperative anxiety.

Study 4, Gabapentin reduces preoperative anxiety and pain catastrophizing in highly anxious patients prior to major surgery: A double blind randomized placebo-controlled trial was published on-line on Feb 3rd, 2013 and is scheduled for print in the Canadian Journal of Anesthesia, May 2013. Permission to reproduce this manuscript has been obtained from the publisher. This study was also presented at the 10th IASP Research Symposium on Pain Genetics, in Miami, Florida, U.S.A. Feb 7th – 9th, 2012. I’d like to again thank statistician Nicholas Mitsakakis for his involvement with the current chapter.
7 Gabapentin Reduces Preoperative Anxiety and Pain Catastrophizing in Highly Anxious Patients prior to Major Surgery

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7.1 Abstract

Introduction: Gabapentin is increasingly being used for the treatment of postoperative pain and a variety of psychiatric diseases including chronic anxiety disorders. Trials have reported mixed results when gabapentin has been administered for the treatment of preoperative anxiety. We tested the hypothesis that gabapentin 1200mg versus placebo would reduce preoperative anxiety in patients who exhibit moderate to high preoperative anxiety.

Methods: A blinded, randomized, controlled trial was conducted between September 2009 and June 2011 at the Toronto General Hospital. Following ethics approval and informed consent, 50 female patients with a 0 – 10 numeric rating scale (NRS) anxiety score of greater than or equal to 5/10 consented to receive either gabapentin 1200 mg (n=25) or placebo (n=25) prior to surgery. Randomization was computer-generated, and the Investigational Pharmacy was responsible for the blinding and dispensing of medication. All patients and care providers, including physicians, nurses and study personnel, were blinded to group allocation. Before administering the study medication, baseline anxiety levels were measured using a NRS, the Spielberger State and Trait Anxiety Inventories, the Pain Catastrophizing Scale and the Pain Anxiety Symptoms Scale-20. Baseline pain intensity (0-10 NRS) and level of sedation (0-10 NRS and Richmond Agitation-Sedation Scale (RASS)) were also measured.
Two hours after the administration of gabapentin or placebo, and prior to surgery, patients again rated their anxiety, pain and sedation levels using the same measurement tools as at baseline. The main outcome was a reduction in preoperative anxiety.

Results: 44 patients (22 gabapentin 1200 mg treated & 22 placebo treated) were included in the analysis of the primary outcome. Analysis of covariance (ANCOVA) in which pre-drug NRS anxiety scores were used as the covariate, showed that post-drug preoperative NRS anxiety (1.44 (0.19-2.70)) and pain catastrophizing (0.43 (0.12-0.74)) scores were significantly lower in the gabapentin group compared with the placebo control group. Post-drug sedation (-3.02 (-4.28, -1.77) and Richmond Agitation-Sedation Scale (0.41 (0.12, 0.71)) scores were significantly more (greater sedation) in the gabapentin group than the placebo group.

Conclusions: Administration of gabapentin 1200 mg prior to surgery reduces preoperative NRS anxiety scores, pain catastrophizing scores and increases sedation prior to entering the operating room. These results suggest that gabapentin 1200 mg may be a treatment option for patients who exhibit high levels of preoperative anxiety and pain catastrophizing, however the sedative properties of the medication and the possibility of delayed postoperative discharge in the elective ambulatory population should be taken into consideration.

7.2 Introduction

Preoperative anxiety is a clinically significant problem for many patients undergoing surgery. Intense preoperative anxiety and fear-based states are associated with a higher intensity of acute postoperative pain (Katz, et al., 2008b) and the development of chronic postsurgical pain (Forsythe, et al., 2008; Harden, et al., 2003). Benzodiazepines are first-line treatments for patients who exhibit clinically significant preoperative anxiety (Giacalone,
1992; Wright, et al., 2007). Although novel anti-anxiety techniques/agents continue to be investigated for the pediatric population (Almenrader, et al., 2007; Golan, et al., 2009), there have been very few studies examining novel pharmacological interventions for the treatment of preoperative anxiety in adults.

Recent studies suggest that gabapentin and pregabalin, which are \( \alpha_2\delta \) (alpha-2-delta) voltage-dependent calcium channel blockers, may be effective for preoperative anxiolysis. However, these studies have produced mixed results (Clarke, et al., 2010; Menigaux, et al., 2005; Tirault, et al., 2010). Patients who received gabapentin 1200 mg prior to anterior cruciate ligament repair reported less preoperative anxiety on the operating table prior to the induction of anesthesia compared with patients who received placebo medications (Menigaux, et al., 2005). In other studies, gabapentin 1200 mg did not reduce preoperative anxiety when compared to the benzodiazepine, oxazepam (15 mg) in patients undergoing vaginal hysterectomy (Rorarius, et al., 2004), nor did gabapentin 600 mg provide anxiolysis prior to total hip arthroplasty when administered 2 hours prior to induction of anesthesia (Clarke, et al., 2010). Two of these studies did not include pre-drug baseline anxiety scores (Menigaux, et al., 2005; Rorarius, et al., 2004), one failed to include an appropriate placebo-control condition (Rorarius, et al., 2004), and another recruited patients with low levels of preoperative anxiety (Clarke, et al., 2010).

Taken together the results of the four published studies are equivocal. Two studies lacked pre-drug baseline anxiety scores (Menigaux, et al., 2005; Rorarius, et al., 2004), raising the possibility that the two groups differed in preoperative anxiety prior to the intervention. One study lacked an appropriate placebo-control condition (Rorarius, et al., 2004) which may have masked an effect by the two active medications (gabapentin vs.
oxazepam) when compared to placebo. The final two studies included patients with low levels of preoperative anxiety (Clarke, et al., 2010; Tirault, et al. 2010), suggesting a floor effect in which there was little room for gabapentin to reduce anxiety. A summary of previous results is presented (Table 7.1).

**Table 7.1 Comparison of Previous Studies looking at Gabapentin for Preoperative Anxiety**

<table>
<thead>
<tr>
<th>Study*</th>
<th>Surgery Population</th>
<th>Intervention</th>
<th>Treatment Effect and CI (95% CI)</th>
<th>Interpretation</th>
<th>Problem with Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rorarius et al. (2004)</td>
<td>Vaginal Hysterectomy Total n= 75</td>
<td>Gabapentin: 1200mg (n=38) vs. 15 mg of Oxazepam (n=37)</td>
<td>Control: 10.0 mm (0 – 24.5) vs. Gabapentin: 20.0 (10–41.25)*</td>
<td>No difference in preoperative anxiety between patients that received gabapentin or oxazepam.</td>
<td>Lack of a placebo control group.</td>
</tr>
<tr>
<td>Menigaux et al. (2005)</td>
<td>ACL Repair Total n=40</td>
<td>Gabapentin 1200 mg (n=20) vs. Placebo (n=20)</td>
<td>38.0mm (28.4 mm to 47.6 mm)</td>
<td>Patients that received gabapentin had significantly less preoperative anxiety compared to placebo.</td>
<td>Lack of baseline anxiety measurement.</td>
</tr>
<tr>
<td>Clarke et al. (2010)</td>
<td>Total Hip Arthroplasty n=70</td>
<td>Gabapentin 600 mg (n=22) vs. Placebo (n=48)</td>
<td>3.99 mm (-1.15 mm to 9.13 mm)</td>
<td>No difference in preoperative anxiolysis between patients that received gabapentin and placebo.</td>
<td>Low baseline levels of anxiety.</td>
</tr>
</tbody>
</table>
Tirault et al. (2010) conducted a Mixed Surgical cohort study involving 210 patients, randomized into three groups: Gabapentin 1200 mg (n=66) vs. Placebo (n=69) vs. Hydroxyzine 75 mg (n=66). The results showed that patients who received Gabapentin had significantly lower preoperative anxiety in the holding area and before induction than patients who received either hydroxyzine or placebo. Anxiety decreased significantly over time only in the Gabapentin group.

* Study reports scores for control and Gabapentin groups only as medians and interquartile Ranges.

Differences among the studies in the dose of Gabapentin administered and methodological problems leave the question unanswered as to whether Gabapentin has anxiolytic effects when used pre-operatively.

The present randomized, placebo-controlled, double-blinded trial provides a methodological improvement on previous work performed in the area. First, we measured anxiety prior to drug administration to ensure that any post-drug differences were not due to pre-existing levels of anxiety. Second, we selected a patient population that exhibited moderate to high levels of preoperative anxiety; previous trials have not screened patients for preoperative anxiety. Anxious patients tend to require longer postoperative hospital stays, and can develop cognitive and behavioural sequelae that may have significant negative effects on recovery (Rolfson, Dahlberg, Nilsson, Malchau, & Garellick, 2009). Young, anxious female patients have been shown to be at an especially high risk of developing perioperative psychological and physical surgical stress reactions (Rosen, Svensson, & Nilsson, 2008; Sun,
Beyond anxiety related to the experience of pain in the postoperative period, certain psychological states have also predicted the need for increased postoperative care. Pain catastrophizing is associated with a multitude of pain-related outcomes including pain severity, decreased pain tolerance, increased postsurgical pain, increased analgesic consumption and somatization (Edwards, Bingham, Bathon, & Haythornthwaite, 2006; Haythornthwaite, Clark, Pappagallo, & Raja, 2003; Roth, Tripp, Harrison, Sullivan, & Carson, 2007; Sullivan, Thorn, Haythornthwaite, Keefe, Martin, Bradley, & Lefebvre, 2001). High levels of pain-related anxiety has also been associated with greater pain severity, disability and lower quality of life (Ocanez, McHugh, & Otto, 2010). Patient factors, such as female gender and younger age, are correlated with heightened fear-based states, which lead to increased perioperative pain and anxiety (Anagnostopoulou, Stroumpoulis, Baltayiannis, Voyagis, Haniotis, Iacovidou, Papadimitriou, & Xanthos, 2011; Perks, Chakravarti, & Manninen, 2009; Sun, et al., 2008; Valenzuela Millan, Barrera Serrano, & Ornelas Aguirre, 2010).

The aim of the present randomized, placebo-controlled, double-blinded trial was to compare the anxiety-reducing effects of gabapentin with a placebo in moderate to highly anxious female patients about to undergo surgery. Secondary aims included (1) evaluating the magnitude of the linear relationships among the anxiety variables and (2) comparing the two groups in terms of sedation scores, RASS scores and NRS pain scores. The STAI-S and STAI-T are the “gold standards” for measuring state and trait anxiety respectively. The items STAI-S and STAI-T were included in the present study to be more rigorous in the assessment of preoperative anxiety than simply using a one item measure like the NRS. Correlations were computed to ensure that the NRS for anxiety and the STAI-S and STAI-T were, in fact, measuring a similar construct. Between group comparisons were conducted to determine
whether gabapentin affected sedation and pain.

7.3 Methods

The study was reviewed and approved by the Research Ethics Board of the Toronto General Hospital, University Health Network (Toronto, Ontario) on June 19th 2009. Signed informed consent was obtained from each participant at the time of recruitment. The present study was a single-centre, randomized, placebo-controlled, blinded trial.

Study population

Female participants between 18 and 50 years of age with an American Society of Anesthesiologists (ASA) physical status score of I, II or III who were scheduled for non-cardiac surgery and who reported a preoperative anxiety score of greater than or equal to 5 out of 10 on the 11 point NRS for anxiety were eligible to participate. Exclusion criteria were the inability to understand English or to provide informed consent, a known allergy to gabapentin, abnormal liver or renal function, known HIV, hepatitis B or hepatitis C infection, severe mental illness, and diabetic patients on insulin or with impaired renal function (creatinine level >106 µmol/L). Subjects who were currently taking either gabapentin or pregabalin, were pregnant or breastfeeding, or with a history of drug or alcohol abuse were also excluded.

Drug preparation, dispensing, and randomization

A randomization schedule, using permuted blocks of varying size (4, 6, and 8) (StatsDirect Statistical Software (version 2.7.5) (Cheshire, UK)) and specifying the group (gabapentin 1200 mg or placebo) to which participants were to be allocated, was generated by an investigator (JK) not otherwise involved with the participants, data collection or data
analysis. The randomization schedule was provided to the Toronto General Hospital Investigational Pharmacy that was responsible for the blinding and dispensing of medication. The gabapentin was encapsulated in colored gelatin capsules identical in all respects to the placebo capsules which contained lactose monohydrate. The capsules were dispensed into sequentially numbered, identical containers according to the allocation sequence in the randomization schedule. All patients and care providers, including physicians, nurses and study personnel, were blinded to group allocation.

Potential participants were approached approximately 1 week before surgery in the preanesthetic clinic to determine their eligibility for participation. The NRS for anxiety was administered to patients to determine eligibility (i.e., a score of greater than 5 out of 10 on the NRS for anxiety) and is not the standard of practice at our institution. After obtaining informed consent, pre-admission pain questionnaires (i.e., the NRS pain score and McGill Pain Questionnaire (SF-MPQ-2)) were administered. Consenting participants were then instructed to arrive 2.5 hours prior to their scheduled surgery. Upon arrival to the hospital on the day of surgery, pre-drug administration questionnaires were completed followed by administration of the study drug that had been prepared and dispensed by the investigational pharmacy. Participants were then monitored continuously in the preoperative facility by qualified nursing staff. Two hours after ingestion of the study drug, the questionnaires that had been completed prior to taking the drug, were re-administered to the participants.

The choice of anesthetic technique, induction and intraoperative medications were left to the discretion of the attending anesthesiologist who had been informed that the participant was in a research study and had received either gabapentin 1200 mg or an inert placebo.

Procedure
In addition to the commonly used visual analogue scale (NRS) measurement tool administered for anxiety in the perioperative environment, the Spielberger State and Trait Anxiety Inventories (STAI-S and STAI-T) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), the Pain Catastrophizing Scale (PCS) (Sullivan, Bishop, & Pivik, 1995) and the Pain Anxiety Symptoms Scale (PASS) (McCracken, Zayfert, & Gross, 1992) were administered to assess the efficacy of gabapentin administration for the treatment of preoperative anxiety in young, healthy women prior to major surgery. Anxiety level was measured using a 0 to 10 NRS and the STAI-S and STAI-T (Spielberger, et al., 1983). The pain-anxiety relationship was assessed by the PASS and the PCS. All measures were administered upon arrival to hospital (pre-treatment) and two hours postdrug administration (post-treatment). NRS scores for pain and sedation were completed one hour after the end of surgery while the patients were in the postoperative anesthetic care unit. Finally, the adverse effects of sedation and agitation were measured using the Richmond Agitation-Sedation Scale (RASS) administered by the study coordinator at pretreatment, post-treatment and 1 hour postsurgery in the postanesthetic care unit (PACU) (Sessler, Gosnell, Grap, Brophy, O'Neal, Keane, Tesoro, & Elswick, 2002). Appendix A outlines in detail the anxiety instruments used in this study, for these measures higher scores represent greater anxiety. The RASS measurement tool is outlined in Appendix B, a lower score (i.e. a negative score) on this measurement tool denotes greater sedation.

Sample Size Estimate

Previous work in a sample of 40 patients (N=20 patients per group) found that preoperative anxiety scores as measured by a 100 mm visual analogue scale (VAS) were significantly lower in gabapentin treated patients compared to patients that received placebo (28 ± 16
versus 66 ± 15 mm, respectively; p=0.0001) (Menigaux, et al., 2005). Using the above data, we estimated that a sample size of 4 patients per group would be required to detect a mean difference of 34 mm by two-tailed t-test, using a standard deviation of 16 mm, a Type 1 error rate of 0.05 (2sided) and a power of 0.80. This sample size seemed unrealistically small largely because of what appeared to us to be a very small standard deviation. We also estimated sample size from data showing that gabapentin reduced pre-operative anxiety (20 mm ± 21) in comparison with a placebo control group (36 ± 28) (Tirault et al 2010) which indicated that 29 patients per group would be needed to detect a 16 mm difference in anxiety with alpha = 0.05 (2 sided) and power = 0.8 (Tirault, et al., 2010). Based on the two studies cited above, and given that our primary outcome was a clinically significant decrease in anxiety measured as by the NRS, we recruited 25 patients per group (i.e., using an expected mean difference of 20 mm and a pooled standard deviation of 21 from the Tirault study). There were no patients lost to follow-up given the primary outcome was collected prior to surgery and data collection ended 1 hour following surgery. A mean difference of 20 mm would represent at minimum, a 20% clinically significant reduction in preoperative anxiety.

Statistical analysis

Clinical and demographic variables were described with means and standard deviations for continuous data, and frequencies and percentages for categorical data and compared between the groups with t-test and chi-squared tests, respectively. Summary scores from the different questionnaires were described using medians and interquartile ranges. Post-treatment scores were compared between groups using analysis of covariance (ANCOVA) with treatment group and baseline scores included as covariates. Data analysis was performed by a biostatistician (NM) not otherwise involved in the trial using SAS statistical software package

7.4 Results

Recruitment and retention of patients

Patients were recruited between September 2009 and June 2011. A flow chart outlining the recruitment and retention of study patients is shown in Figure 7.2. Overall, 187 patients were screened for eligibility. Of these, 70 patients did not meet the inclusion criteria (see Figure 7.2) and 67 patients declined participation. Of the 50 women randomly assigned to the two study groups, 44 patients completed the in-hospital protocol. Six patients did not have sufficient time to complete the post-treatment set of study questionnaires and were taken to the operating room expeditiously (see Figure 7.2).

Figure 7.2 Patient Enrollment and Study Flow. pt = Patient(s)
Assessed for eligibility

(n=187)

Excluded

Declined participation (n=67); anxiety score <5/10 (n=38); already involved in another trial (n=9); diabetes and/or an elevated creatinine level (n=3); liver dysfunction/hepatitis C (n=3); Age older than 50 years (n=1); psychiatric disorder (n=4); breastfeeding mother (n=3); language barrier (n=7); already taking gabapentin (n=2)

Randomized

(n=50)

Group I
Placebo
(n=25)

Excluded:

n = 3 – insufficient time given to complete the second set of study questionnaires (< two hours) after taking the study medications

Completed protocol and analyzed

(n=22)

Group II
Gabapentin 1200mg
(n=25)

Excluded:

n = 3 - insufficient time given to complete the second set of study questionnaires (< two hours) after taking the study medications

Completed protocol and analyzed

(n=22)
**Demographic and clinical variables**

The two groups were comparable with respect to age, body mass index, types of surgery, initial pain and anxiety scores at the time of enrollment, duration of surgery and intraoperative opioid use (Table 7.2).

**Table 7.2 Baseline Demographic Information and Enrollment Scores**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GABAPENTIN 1200 mg (n = 22)</td>
</tr>
<tr>
<td></td>
<td>PLACEBO (n = 22)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.6 ± 6.6</td>
</tr>
<tr>
<td></td>
<td>41.8 ± 6.8</td>
</tr>
<tr>
<td>Body mass index (kg/m^2)</td>
<td>29.7 ± 11.1</td>
</tr>
<tr>
<td></td>
<td>29.6 ± 9.3</td>
</tr>
<tr>
<td>0-10 NRS Anxiety score at enrollment</td>
<td>7.0 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>6.9 ± 1.3</td>
</tr>
<tr>
<td>0-10 NRS Pain score at enrollment</td>
<td>0.7 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>1.5 ± 2.4</td>
</tr>
<tr>
<td>McGill Pain score at enrollment</td>
<td>1.1 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>1.4 ± 1.4</td>
</tr>
<tr>
<td>Type of surgery: n</td>
<td>General: 6</td>
</tr>
<tr>
<td></td>
<td>Gynecological: 8</td>
</tr>
<tr>
<td></td>
<td>Plastics: 5</td>
</tr>
<tr>
<td></td>
<td>Ear nose &amp; throat: 3</td>
</tr>
<tr>
<td></td>
<td>General: 8</td>
</tr>
<tr>
<td></td>
<td>Gynecological: 8</td>
</tr>
<tr>
<td></td>
<td>Plastics: 3</td>
</tr>
<tr>
<td></td>
<td>Ear nose &amp; throat: 3</td>
</tr>
<tr>
<td>Duration of surgery (hrs)</td>
<td>5.6 ± 3.2</td>
</tr>
<tr>
<td></td>
<td>4.5 ± 2.7</td>
</tr>
<tr>
<td>Intraoperative Opioids administered</td>
<td>Fentanyl (mcg): 247.7 ± 156.9</td>
</tr>
<tr>
<td></td>
<td>Fentanyl (mcg): 259.1 ± 66.6</td>
</tr>
<tr>
<td></td>
<td>Morphine (mg): 6.3 ± 6.3</td>
</tr>
<tr>
<td></td>
<td>Morphine (mg): 5.6 ± 6.8</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD unless otherwise indicated. hrs = Hours; NRS = Numerical rating scale.

**Gabapentin anxiolysis intervention**

Table 7.3 shows the median and interquartile ranges, as well as, point and interval estimates of the study outcome measures for the two groups before and two hours after administration of the study drug preoperatively. ANCOVA showed that NRS anxiety scores and PCS scores
were clinically lower in the gabapentin group than the placebo group. Prior to entering the operating room, NRS sedation scores and RASS scores found clinically more sedation in the gabapentin group compared to the placebo group. Prior to entering the operating room, 10 patients in the gabapentin group reported a NRS sedation score ≥8/10 vs. 2 in the placebo group (p<0.05). The RASS score demonstrated drowsiness in 8 patients that received gabapentin vs. 2 that received placebo (p<0.05).

**Table 7.3 Anxiety, pain and sedation scores for the two groups before (pre-treatment) and two hours after (post-treatment) administration of placebo or gabapentin prior to surgery**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Gabapentin 1200 mg (n=22)</th>
<th>Placebo (n=22)</th>
<th>Effect Size &amp; Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety Score (NRS)</td>
<td>Pre-treatment score 5.5 (2.0 – 7.0)</td>
<td>Post-treatment score 2.5 (1.0 – 4.0)</td>
<td>Pre-treatment score 6.0 (3.5 – 8.0)</td>
</tr>
<tr>
<td>McGill Pain Questionnaire</td>
<td>Pre-treatment score 1.5 (0.1 – 2.0)</td>
<td>Post-treatment score 0.6 (0.1 – 1.2)</td>
<td>Pre-treatment score 1.0 (0.1 – 1.9)</td>
</tr>
<tr>
<td>Pain Catastrophizing</td>
<td>Pre-treatment score 19.5 (11.7 – 29.9)</td>
<td>Post-treatment score 13.0 (6.5 – 24.7)</td>
<td>Pre-treatment score 20.8 (10.4 – 29.9)</td>
</tr>
<tr>
<td>Spielberger – Trait</td>
<td>Pre-treatment score 37.5 (29.0 – 47.0)</td>
<td>Post-treatment score 35.5 (30.0 – 44.0)</td>
<td>Pre-treatment score 36.0 (30.0 – 46.0)</td>
</tr>
<tr>
<td>Spielberger –  Trait</td>
<td>Pre-treatment score 46.0 (40.0 – 55.0)</td>
<td>Post-treatment score 40.0 (32.0 – 49.0)</td>
<td>Pre-treatment score 48.0 (40.0 – 58.5)</td>
</tr>
<tr>
<td>State</td>
<td>Pain Anxiety Symptoms Scale</td>
<td>Pain Score (NRS)</td>
<td>Sedation Score (NRS)</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>----------------------------</td>
<td>------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td></td>
<td>33.5 (23.0 – 50.0)</td>
<td>0.0 (0.0 – 1.0)</td>
<td>2 (0.0 – 6.0)</td>
</tr>
<tr>
<td></td>
<td>28.0 (13.0 – 39.0)</td>
<td>0.0 (0.0 – 1.0)</td>
<td>7 (5.0 – 8.0)</td>
</tr>
<tr>
<td></td>
<td>39.0 (23.0 – 55.5)</td>
<td>0.0 (0.0 – 1.5)</td>
<td>2.0 (0.0 – 5.0)</td>
</tr>
<tr>
<td></td>
<td>30.5 (20.0 – 48.0)</td>
<td>0.0 (0.0 – 2.0)</td>
<td>5 (2.0 – 8.0)</td>
</tr>
</tbody>
</table>

Data presented as median (interquartile range). NRS Numerical rating scale

The largest Spearman correlation coefficient involving the NRS-anxiety, both before and after drug administration, was with the STAIS (before: \( r (42) = 0.64, p = 3.33E-06 \), and after: \( r (42) = 0.66, p = 8.49E-07 \), respectively). In contrast, Spearman correlations between the NRS-anxiety and pre-drug total scores on the PASS-20 \( r (42) = 0.41, p = 0.005 \) and PCS \( r (42) = 0.55, p = 0.0001 \) were considerably larger than post-drug correlation coefficients \( \text{PASS-20, } r (42) = 0.16, p = 0.30 \text{ and PCS, } r (42) = 0.21 \text{, } p = 0.17 \). These findings provide initial support for the construct and discriminative validity of the NRS-anxiety as a measure of state anxiety in the pre-surgical setting.
In the post-anesthetic care unit after surgery, NRS sedation scores \( p=0.01 \) and RASS scores were clinically higher in gabapentin-treated than placebo treated-patients. No difference in postoperative pain was noted in the PACU (Table 4). Furthermore, 16 patients in the gabapentin group reported a NRS sedation score \( \geq 8/10 \) vs. 9 in the placebo group \( p<0.05 \). The RASS demonstrated sedation (i.e. a RASS score \( \leq -2 \)) in 8 patients that received gabapentin vs. 3 that received placebo (Table 7.4).

**Table 7.4 Pain and sedation scores for the two groups in the postanesthetic care unit (PACU) one hour after surgery**

<table>
<thead>
<tr>
<th></th>
<th>GABAPENTIN 1200mg (n = 22)</th>
<th>PLACEBO (n = 22)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioids administered</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with the first hour of arrival to the PACU</td>
<td>Fentanyl (mcg): 8.0 ± 19.0*</td>
<td>Fentanyl (mcg): 25.7 ± 36.3</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Morphine (mg): 0.8 ± 2.1</td>
<td>Morphine (mg): 1.3 ± 2.8</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>NRS Pain score</strong></td>
<td>4.5 (2.0 – 6.0)</td>
<td>5.0 (2.0 – 7.0)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>NRS Sedation score</strong></td>
<td>8.5 (7.0 – 9.0)*</td>
<td>8.0 (5.0 – 9.0)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Richmond Agitation - Sedation Scale</strong></td>
<td>-1.0 (-2.0 – -1.0)*</td>
<td>-1.0 (-1.5 – -0.5)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data presented as median (interquartile range). *Statistically significant (ie, \( p<0.05 \)). NRS = Numerical rating scale

### 7.5 Discussion

The aim of the present trial was to compare the anxiety-reducing effects of 1200 mg of gabapentin to placebo in moderate to highly anxious patients about to undergo major surgery. Our results indicate that 1200 mg gabapentin produced clinically significant anxiolysis and lower levels of pain catastrophizing in a female population that exhibited moderate to high anxiety prior to major surgery (Table 7.3). The present results are consistent with previous studies using 1200 mg of gabapentin (Menigaux, et al., 2005) as well as with 150-300 mg of pregabalin (Gonano, Latzke, Sabeti-Aschraf, Kettner, Chiari, & Gustorff, 2009; Spreng,
Dahl, & Raeder, 2011; White, et al., 2009a), showing lower anxiety levels compared with a placebo. In contrast, the present results conflict with our previous trial using gabapentin 600 mg which did not reduce anxiety prior to hip arthroplasty. It is possible that doses lower than 1200 mg do not reach the therapeutic plasma levels needed to produce clinical anxiolytic effects (Beydoun, et al., 1995; Su, et al., 1995). Furthermore, the documentation of preoperative anxiety prior to enrollment was not undertaken in previous work (Menigaux, et al., 2005; Rorarius, et al., 2004).

Biopsychosocial models have suggested that to understand pain-related outcomes, psychological outcomes must be considered in addition to physical outcomes (Keefe & France, 1999). Pain catastrophizing is described as the extent to which individuals worry, amplify and feel helpless about their current or anticipated pain experience (Sullivan, et al., 1995). There is general consensus that catastrophizing involves an exaggerated negative orientation toward noxious stimuli (Sullivan, et al., 1995). Psychological stressors, such as fears surrounding intense pain are common prior to major surgery (Pritchard, 2009). Thus, the tendency to catastrophize about the impending surgical experience and anticipated pain increases distress and may contribute to a more intense pain experience (Sullivan, et al., 2001). As anxiety increases preoperatively, patient preoperative quality of life suffers inversely (Anagnostopoulou, et al., 2011). Recent studies have revealed that presurgical pain catastrophizing is a unique predictor of immediate postsurgical pain and the severity of pain up to six weeks after surgery (Sullivan, et al., 2009), furthermore, increased pain catastrophizing predicted increased pain and poor function one year following total knee arthroplasty (Sullivan, Tanzer, Reardon, Amirault, Dunbar, & Stanish, 2011). Our data are the first to suggest that gabapentin may play a role in the reduction of pain catastrophizing and help reduce the negative affect caused by such thinking. Future studies might investigate
pharmacological interventions aimed at decreasing pain catastrophizing to determine whether patients benefit with respect to an improvement in postsurgical pain and possible postoperative patient function.

It is interesting to note that we found a clinically significant difference between the two groups as measured by the NRS-anxiety but not in state anxiety as measured by the gold standard, Spielberger Anxiety Inventory (STAI). Scores on the NRS-anxiety and PCS were statistically significantly lower in the gabapentin group than the placebo group two hours after drug administration suggesting that gabapentin may have specific effects on pre-surgical anxiety as measured by the NRS-anxiety and on pre-surgical pain catastrophizing. The absence of an effect for pain anxiety and trait anxiety is consistent with the non-significant, post-drug correlations between the NRS-A and these variables. Gabapentin failed to decrease scores on the STAI-S or the PASS. The STAI-S scale evaluates how respondents feel “right now, at this moment. These results suggest that the VAS measurement tool for preoperative anxiety may, in fact, be a more sensitive measurement tool in the perioperative time period than the STAI (Spielberger, et al., 1983), which is considered the gold standard for psychological assessment of high anxiety states in the psychological community. In our study, it is difficult to explain the absence of evidence for post-drug differences between the groups on the STAIS. However, these results and the relationship with gabapentin administration should be explored in future studies.

Many studies have examined the use of gabapentin for postoperative pain in the perioperative period. Given that pain was a secondary outcome (evaluated by the NRS at the 1 hour isolated time point) no conclusions can be drawn based on the lack of an early pain reduction. Many studies have reported improved postoperative pain scores well beyond the 1
hour time point and reported opioid sparing and pain reductions for hours (Pandey, et al., 2004b) and up to several days (Clarke, et al., 2009b) after surgery which this study was not designed to assess. In contrast, only two (Clarke, et al., 2009a; Moore, et al., 2011) have rigorously documented the adverse-effects profiles associated with these medications. In the present study, patients who received gabapentin reported an increase in sedation prior to entering the operating room (Table 3). Anesthesiologists might agree that an increase in sedation prior to the induction of anesthesia is a benefit as long as it is not accompanied by respiratory depression or a clinically significant decrease in the level of patient consciousness. None of the patients who received gabapentin were sedated to a point that compromised their care; every patient was sufficiently alert to complete the questionnaires 2 hours after study drug administration. However, given the effect size of gabapentin on the self-report NRS sedation scores it is possible that gabapentin may be more sedating than anxiolytic in the preoperative time period, leading to a possible explanation for the lack of an effect on the STAIS. Clinically, gabapentin 1200 mg appears to be safe as a preoperative adjunct and has been administered without significant adverse events in many previous trials. The observed RASS scores were congruent with the increase in sedation reported by patients (Table 3) after the administration of the second set of questionnaires before they entered the operating room. Table 4 demonstrates that gabapentin-treated patients were clinically more sedated 1 hour after surgery in the PACU compared to placebo-treated patients. Although sedation levels were higher 1 hour after surgery in patients who received gabapentin, no adverse events were reported, PACU stay was not prolonged, and clinical care was not compromised. It is important to point out that that the total dose of intraoperative opioids and the opioids given within the first hour of arrival to the PACU were similar in both groups and therefore the difference in sedation noted in the PACU is unlikely due to intra and post-
operative opioid use. Given that 1200 mg of gabapentin is a relatively high preoperative dose, the increased sedation which was evident postoperatively should be taken into consideration when using this medication for moderate to severe preoperative anxiety. 1200 mg of gabapentin administered routinely in the ambulatory setting may delay discharge.

The proposed mechanism of action of gabapentin and pregabalin is believed to be selective inhibitory binding to the alpha-2-delta (α2δ) subunit of voltage-dependent calcium channels in activated neurons (Taylor, 2009). However, there is emerging evidence that these compounds may interact with other molecular targets within the central nervous system (CNS) (Bonin, et al., 2011). Gabapentin was initially developed to mimic the actions of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). A cyclohexane ring was added to the carbon backbone of GABA to facilitate the transfer of the drug across the blood-brain barrier (Goa & Sorkin, 1993). Surprisingly, gabapentin does not bind to or directly modulate GABA_A receptors (Cheng, et al., 2006; Macdonald & Greenfield, 1997; Rock, et al., 1993), nor does it modulate GABA_B receptors, except at high concentrations (Sills, 2006). However, in healthy volunteers and studies involving patients with epilepsy, GABA levels were increased after oral ingestion of gabapentin (Kuzniecky, Ho, Pan, Martin, Gilliam, Faught, & Hetherington, 2002; Petroff, Rothman, Behar, Lamoureux, & Mattson, 1996). Furthermore, gabapentin was found to inhibit both the excitatory synaptic transmission in vitro (Shimoyama, Shimoyama, & Hori, 2000) and the neuronal response to noxious electrical and mechanical stimulation in vivo mediated by α-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid (AMPA) (Chizh, Scheede, & Schlutz, 2000) and decrease glutamate levels in the rat brain (Errante & Petroff, 2003). The above human and rodent data suggest possible mechanisms underlying both the anxiolytic and sedative properties observed herein.
A limitation to the current study is that we did not control intraoperative anesthesia management and left the care of the patients to the attending anesthesiologist. Second, our sample is comprised of only women, although unlikely, it is possible that these findings may not be relevant to men. Finally, our primary outcome was collected before arrival to the operating room (a change in anxiety after preoperative administration of gabapentin) and the measures of postoperative pain and sedation were included but limited to the first postoperative hour in the PACU.

In summary, gabapentin 1200 mg administered prior to surgery reduced preoperative anxiety as measured by a numeric rating scale but not the STAI-S, and pain catastrophizing two hours later compared with placebo treatment. The gabapentin treated participants also had an increased level of sedation before entering the operating room and were more somnolent 1 hour after surgery. Gabapentin 1200 mg may be considered a treatment option for patients who exhibit high levels of preoperative anxiety and pain catastrophizing, however the sedative properties of the medication and the possibility of delayed postoperative discharge in the elective ambulatory population should be taken into consideration. The results presented in this manuscript need to be evaluated in future RCTs.
Chapter 8

The following General discussion will integrate the findings from the present dissertation with the published literature, discuss the limitations of the dissertation and suggest my view on where the perioperative research field should be moving with respect to reporting of outcomes. I will also briefly explore pregabalin, the physiology and pharmacology of this next generation anticonvulsant with respect to reducing perioperative pain and the possibility that exists that these drugs may help to reduce chronic postsurgical pain. My suggestions for future work, precedes the conclusion of this dissertation.

8.1 General Discussion

The findings from this dissertation provide support for the use of gabapentin in the perioperative setting. Study 1 (chapter 4) provides evidence which is congruent with previous findings that demonstrate a reduction in opioid consumption and an improvement in early functional recovery after total knee arthroplasty when gabapentin is continued into the postoperative time period (Clarke, et al., 2009b). These findings provide evidence to support the hypothesis that improved pain control can lead to an improvement in functional rehabilitation. In study 4 (chapter 7), novel information was presented which supports the preoperative use of gabapentin for anxiolysis in patients with moderate to high levels of preoperative anxiety undergoing major surgery (chapter 7).

Study 2 (chapter 5) and study 3 (chapter 6) presented novel findings regarding the use of a single preoperative dose of 600 mg of gabapentin. Study 2 clearly demonstrated that the addition of a single dose of 600 mg of gabapentin did not reduce opioid consumption, nor
was it sufficient to reduce acute or chronic pain (Clarke, et al., 2009a). Regardless of the
timing of the medication (i.e. before surgery or immediately in the PACU) this dose of
gabapentin did not reduce pain scores or opioid consumption when added to a robust
multimodal analgesic regimen.

Upon designing these studies we had several objectives in mind, it is clear that we have
answered some of these objectives but a few remain unanswered. The primary objective of
the first study was to accomplish a dose response relationship with respect to gabapentin,
pain, opioid consumption and functional outcomes. Given that a dose response analysis was
not feasible, our planned contrasts aimed to test the following hypotheses: (1) Patients
continued on gabapentin postoperatively will require less opioid pain medication compared to
patients that receive placebo medication and (2) Patients receiving postoperative gabapentin
will have improved function while performing physiotherapy tasks (i.e. active assisted knee
flexion). With respect to the above hypotheses, it was clear that continuing gabapentin into
the postoperative setting did decrease opioid consumption and demonstrated on average a
greater than 10 degree improvement in active assisted knee flexion on POD 2 and 3 (p<0.05).

Study 2 examined whether: (1) a single dose of gabapentin (600 mg) administration reduced
pain and opioid use after total hip arthroplasty using a multimodal analgesic regimen that
included spinal anesthesia; and whether (2) preoperative administration of gabapentin is more
effective than postoperative administration. Our results demonstrated that whether a 600 mg
dose of gabapentin was given preoperatively or postoperatively, patients’ postoperative
morphine consumption or pain scores were not reduced in hospital nor was there a reduction
in pain 6 months after hip arthroplasty. There are several reasons for the conflicting results
between studies 1 and 2. Clearly continuing gabapentin into the postoperative period is
important with respect to decreasing opioid consumption and improving function, however, the addition of the robust multimodal analgesia regimen and the excellent pain control afforded patients via the additional NSAIDS, acetaminophen, dexamethasone and regional anesthesia cannot be understated. It is also recognized that THA replacement is associated with less acute pain than TKA replacement.

Finally, studies 3 and 4 examined the effectiveness of gabapentin for the treatment of preoperative anxiety. Patients in study 3 did not demonstrate a reduction in preoperative anxiety prior to undergoing their THA. However as noted in chapter 7, the severity of preoperative anxiety prior to their total hip arthroplasty was very low. Therefore, we made significant methodological improvements compared to previous work with the design of study 4. Our objective was to test 1200 mg of gabapentin in a highly anxious population undergoing major surgery and receiving a general anesthetic in order to determine whether or not a reduction in preoperative anxiety was possible. The results of this study were positive and a reduction in not only preoperative anxiety was found, but patients also demonstrated a decrease in pain catastrophizing scores. Study 4 also highlighted an increase in sedation both preoperatively and 1 hour postoperatively in the PACU for patients that received gabapentin. When patients were asked to rate their sedation, the magnitude of this effect was markedly greater in comparison to the blinded observer and may shed some insight into the often under reporting of sedation that accompanies much of the gabapentin perioperative literature.

Overall, we were able to make conclusions based on the objectives put forth at the start of this dissertation. In particular, demonstrating the anxiolytic effect of gabapentin in a population with moderate to severe preoperative anxiety is the highlight of the current work.
However, more work is needed that focuses on the optimal dose and duration of perioperative gabapentin (and pregabalin), with the aim of improving functional outcomes and perhaps leading to decrease the incidence and severity chronic post-surgical pain.

8.2 Limitations

There are several limitations to the series of studies presented in this dissertation. First, 600 mg of gabapentin failed to show a significant effect with respect to reduction of pain, opioid consumption or anxiolysis in studies 2 and 3. It has been well documented that the absorption profile of gabapentin in humans is inconsistent due to the active and saturable α-amino acid transport system (Cheng & Chiou, 2006). Thus, the bioavailability of any given dose varies from 35% – 90% (Cheng & Chiou, 2006). Without plasma samples, one cannot confirm therapeutic drug concentrations of gabapentin, none of our studies tested plasma levels to confirm therapeutic levels. Given the above pharmacokinetics, it is possible that single preoperative doses of gabapentin lower than 1200 mg do not consistently reach the therapeutic plasma levels needed to reduce postoperative opioid use, reduce acute pain or reduce pre-operative anxiolysis. Furthermore, in study 2, the addition of 600 mg of gabapentin to the robust multimodal analgesic regimen may have added minimal antinociceptive effect and did not further reduce the acute pain experienced by patients. It is unclear whether adding 1200 mg of gabapentin to such a regimen would prove to be beneficial to patients given the acute pain scores were in the mild range. Future research could explore this hypothesis.

Intraoperative patient care was not standardized and was left to the discretion of the attending anesthesiologist. Three of the studies in this dissertation (# 2, # 3 and # 4) examined the
effect of a single dose of preoperative gabapentin. A single preoperative dose of gabapentin has been found to reduce postoperative pain and opioid consumption in a variety of surgical procedures (Moore, et al., 2011; Rorarius, et al., 2004; Turan, et al., 2004a; Turan, et al., 2004b). Furthermore, many studies report a reduction in opioid consumption and pain when gabapentin is continued into the acute postoperative period (A. Fassoulaki, et al., 2002b; Gilron, et al., 2005b). Recently, numerous clinical trials have begun to examine the effects of perioperative gabapentin beyond the acute postoperative time period and have suggested that gabapentin has a role in the reduction of chronic post surgical pain (Amr & Yousef, 2010; Sen, et al., 2009a; Sen, et al., 2009b).

Another limitation of the studies in Chapters 4 and 5, was the lack of documentation of preoperative pain characteristics. The incidence of chronic pain reported 6 months after total hip arthroplasty in chapter 5 was 37.8%, given that arthroplasty surgery is often performed to alleviate pain, we are unable to determine if the pain reported at 6 months was less than the pain experienced prior to surgery. The possibility exists that the pain experienced at six months after surgery may be improved from baseline.

8.3 Expanding Perioperative Outcomes

The main outcome measures in most trials of preemptive/preventive analgesia are pain intensity or the presence/absence of pain and analgesic use. It is rare to find a study that is more comprehensive in the outcome measures assessed. Recommendations for assessment of core measures and domains in clinical trials (Dworkin, Turk, Farrar, Haythornthwaite, Jensen, Katz, Kerns, Stucki, Allen, Bellamy, Carr, Chandler, Cowan, Dionne, Galer, Hertz, Jadad, Kramer, Manning, Martin, McCormick, McDermott, McGrath, Quessy, Rappaport, Robbins, Robinson, Rothman, Royal, Simon, Stauffer, Stein, Tollett, Wernicke, & Witter,
include relevant psychological, emotional and physical variables in addition to those routinely assessed (i.e., pain and analgesic use). Assessment of additional domains of physical function and the experience of pain during those functional activities may help to shed light on the predictors of severe acute postoperative pain, the processes involved in recovery from surgery, and the risk factors for developing chronic postsurgical pain. (Katz & Cohen, 2004) Understanding the relationship between a patient’s experience of pain and function, and how to reduce the development of CPSP is critically important, particularly for patients undergoing major surgery.

Using osteoarthritis (OA) as a model, patients suffering from severe OA often suffer months or years of unrelenting activity-related pain. Since there is no cure for OA, treatment strategies focus on alleviating the symptoms (e.g. pain and swelling), while maintaining optimal function. Total joint arthroplasty has emerged as the treatment of choice for patients with severe pain from osteoarthritis. While the common perception is that total joint arthroplasty outcomes are excellent, the reality is that 10-30% of patients (Nikolajsen, Brandsborg, Lucht, Jensen, & Kehlet, 2006)^24 continue to experience pain, and some 20-33% report no functional improvement, even one to two years after their affected joint has been replaced. (Calder, Ashwood, & Hollingdale, 1999; Kennedy, et al., 2002; Konig, Walther, Kirschner, & Gohlke, 2000; Walsh, et al., 1998)

We must develop better measures to evaluate pain in order to identify those at risk of developing chronic post surgical pain after major surgery, and be better able to distinguish the underlying cause of the post operative pain (i.e. infection vs. mechanical vs. neuropathic). These measures include sensory, motor, biomechanical, psychological and physiological markers, in addition to better characterizing the quality and quantity of pain following major surgery. Thus, reducing the incidence of those patients who go on to develop CPSP
following major surgery will require interprofessional collaboration, particularly between anesthesiologists, physical therapists, psychologists, and surgeons.

8.4 Expanding pain interventions beyond the perioperative hospital stay

Given the aging north american population and the pressure to meet targets set forth by governments and hospital administrations with respect to the number of surgeries performed, acute pain practitioners continue to develop aggressive multimodal postoperative strategies. The goals of these aggressive strategies are to improve patient comfort, facilitate early rehabilitation and decrease hospital stay. Given the above trend and the rapid change in clinical practice that can often ensue, it is incumbent that we scientifically examine new interventions and determine whether or not the change in practice improves or to hinders patient outcome. Although the in hospital progress of patients may appear to be more efficient, there is a scarcity of data on pain outcomes and coping beyond the hospital stay. Published data from our institution found that although patients could be discharged prior to POD 5 after total joint replacement surgery, 30% of these patients were not satisfied with their pain control at home (Ramlall, Archibald, Pereira, Sawhney, & Ramlall, 2010). The above evidence suggests that as readiness to discharge time becomes more efficient, physicians should consider aggressive management of postsurgical pain into the take home period. Pain (acute and chronic), function, coping, anxiety and depression outcomes should also be examined beyond the brief postoperative in hospital time period. Studies should consider following patients for greater than 2 months after surgery, the collection of these longterm data would enable the examination of associations between acute postoperative pain interventions and the development of chronic postsurgical pain.
8.5 Future Work

Currently there is an exciting field of research focused on attempting to unravel the complex relationships involved with determining the relative contributions of psychological, environmental, and genetic factors that may predispose patients to transition from acute postoperative pain and develop of chronic post surgical pain syndromes. Preoperative anxiety and fear-based states have been shown to be associated with the intensity of acute postoperative pain and analgesic consumption (Katz, et al., 2008b), as well as the development of chronic postsurgical pain (Forsythe, et al., 2008; Harden, et al., 2003; Sullivan, et al., 2009). A recent meta-analysis has demonstrated that both anxiety and pain catastrophizing may be predictive of the development of chronic post surgical pain (Theunissen, Peters, Bruce, Gramke, & Marcus, 2012). In chapter 7, we demonstrated that 1200 mg of gabapentin decreased pre-operative anxiety and pain catastrophizing and hypothesized that decreasing the negative affect brought about by these cognitive states could also help with the prevention of chronic postsurgical pain. Theunissen and colleagues suggest that routine assessment of anxiety and pain catastrophizing should be incorporated into future studies that investigate transition from acute to chronic postsurgical pain given the increased predictive utility of these measures (Theunissen, et al., 2012).

There is limited evidence to suggest that the α₂δ ligands when given in higher doses, with multiple perioperative administrations and beyond the acute hospital stay (i.e. into the take home period) may effectively reduce the neuropathic pain symptoms involved in the development of chronic neuropathic pain (Buvanendran, Kroin, Della Valle, Kari, Moric, & Tuman, 2010; Carmichael, Katz, Clarke, Kennedy, Kreder, Gollish, & McCartney, 2012). Future research should continue to investigate the optimal dose and duration of therapy of
gabapentin and pregabalin to reduce postoperative pain (both acute and chronic). A detailed examination of the effects of these medications on psychological co-morbidities such as anxiety, depression and catastrophizing is also warranted. Finally, an assessment of physical function and the impact that gabapentin and pregabalin might have on the experience of pain during rehabilitation activities could help to identify patient factors which may impact the recovery process after surgery; these factors may also be associated with the development of chronic post surgical pain. My dissertation has identified some impact with respect to the use of perioperative gabapentin. I am hopeful that future research will continue to examine the optimal role of gabapentin and pregabalin in the perioperative setting and bring us closer to unraveling the complex puzzle associated with the development of acute postoperative pain and the factors that predispose an unfortunate subset of patients to transition thereafter to chronic post surgical pain syndromes.

8.5.1 Pregabalin: Physiology and Pharmacodynamics

Pregabalin is structurally similar to gabapentin (Figure 1.1) and was also marketed primarily for epilepsy and neuropathic pain. Pregabalin (S-[+] -3-isobutylgaba) was designed as a lipophilic g-aminobutyric acid analogue substituted at the 3’ position to facilitate diffusion across the blood-brain barrier (Field, Oles, Lewis, McCleary, Hughes, & Singh, 1997; Gajraj, 2007). Unlike gabapentin, the L-amino transport system, due to the substitution in pregabalin’s molecular structure (Figure 1.1), enables >90% uptake of pregabalin after ingestion (Piyapolrungrong, Li, Bockbrader, Liu, & Fleisher, 2001). The time to maximal drug concentration is 1 to 2 hours and its elimination half-life is approximately 6 hours (Randinitis, Posvar, Alvey, Sedman, Cook, & Bockbrader, 2003). Pregabalin is not protein bound, and it is 92% renally excreted unmetabolized as the parent compound. Pregabalin does not inhibit cytochrome p450 enzymes, nor do these enzymes alter its pharmacokinetics.
Although both gabapentin and pregabalin interact with the α2δ subunit of voltage-dependent calcium channels throughout the nervous system, pregabalin has been found to bind to these receptors with 6 times more potency than gabapentin (Jones & Sorkin, 1998).

Table 8.1 Details several key pharmacokinetic properties of the two medications in animals and humans.

<table>
<thead>
<tr>
<th></th>
<th>GABAPENTIN</th>
<th>PREGABALIN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rodent model –</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticonvulsant activity</td>
<td>9.1 mg/kg (ED 50)</td>
<td>1.3 mg/kg (ED 50)</td>
</tr>
<tr>
<td>threshold</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rodent model –</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathic Pain Activity</td>
<td>10 mg/kg (MED)</td>
<td>3 mg/kg (MED)</td>
</tr>
<tr>
<td><strong>Human –</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half life</td>
<td>5 – 7 hours</td>
<td>5 – 7 hours</td>
</tr>
<tr>
<td><strong>Human –</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Bioavailability</td>
<td>≤50%</td>
<td>≥90%</td>
</tr>
<tr>
<td><strong>Potency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binds to α-2-δ receptor</td>
<td></td>
<td>Binds to α-2-δ receptor with 6 times more potency</td>
</tr>
<tr>
<td><strong>Recommended Daily Dosing Regimen</strong></td>
<td>TID</td>
<td>BID</td>
</tr>
</tbody>
</table>

BID = Twice a day; TID = Three times a day; ED = Effective Dose; MED = Minimal Effective Dose

**8.5.2 Clinical Uses**

Since introduction to the market, pregabalin has demonstrated its clinical efficacy in the treatment of chronic pain conditions such as post-herpetic neuralgia (Dworkin, Corbin, Young, Sharma, LaMoreaux, Bockbrader, Garofalo, & Poole, 2003; Sabatowski, Galvez, Cherry, Jacquot, Vincent, Maisonneuve, & Versavel, 2004), spinal cord pain (Siddall, Cousins,
Otte, Griesing, Chambers, & Murphy, 2006) and fibromyalgia (Crofford, Rowbotham, Mease, Russell, Dworkin, Corbin, Young, LaMoreaux, Martin, & Sharma, 2005). Similar to gabapentin, the “off label” use of pregabalin for postsurgical pain has become a subject of investigation. Pregabalin has been found to be effective at reducing acute postoperative pain after lower limb arthroplasty (Buvanendran, et al., 2010; Mathiesen, et al., 2008), abdominal hysterectomy (Ittichaikulthol, Virankabutra, Kunopart, Khamhom, Putarawuthichai, & Rungphet, 2009; Mathiesen, Rasmussen, Dierking, Lech, Hilsted, Fomsgaard, Lose, & Dahl, 2009), lumbar discectomy (Burke & Shorten, 2010), augmentation mammoplasty (Freedman & O'Hara, 2008) and bariatric surgery (Cabrera Schumley, de la Maza, Ovalle, Farias, & Vives, 2010). As with gabapentin, there is evidence supporting the effectiveness of pregabalin in the treatment of generalized anxiety disorder (Pande, Crockatt, Feltner, Janney, Smith, Weisler, Londborg, Bielski, Zimbroff, Davidson, & Liu-Dumaw, 2003; Strawn & Geracioti, 2007); it also plays a role in improving sleep (Hindmarch, Dawson, & Stanley, 2005; Kubota, Fang, Meltzer, & Krueger, 2001; van Seventer, Feister, Young, Stoker, Versavel, & Rigaudy, 2006). Recent studies have also examined the possible anxiolytic role of pregabalin in the preoperative setting as a possible alternative to benzodiazepines (Nutt, et al., 2009; White, Tufanogullari, Taylor, & Klein, 2009b). In the perioperative period, pregabalin has also been associated with increased levels of sedation, dizziness and diplopia.

8.5.3 Future Role of pregabalin in the prevention of chronic postsurgical pain

There have been three studies examining the preventive effects of perioperative pregabalin administration on the incidence and intensity of chronic post surgical pain (Burke & Shorten, 2010; Buvanendran, et al., 2010; Pesonen, Suojaranta-Ylinen, Hammaren, Kontinen, Raivio, Tarkkila, & Rosenberg, 2011). All three studies showed significant preventive analgesic
effects in that there was a lower incidence of pain and/or lower analgesic requirements at long-term follow-up, ≥2 months after surgery. Buvanendran randomized patients to receive a 300 mg preoperative dose of pregabalin followed by a 14-day twice a day (BID) regimen of pregabalin (50 mg - 150 mg) or placebo following TKA (Buvanendran, et al., 2010). The Leeds Assessment of Neuropathic Symptoms and Signs (Bennett, Smith, Torrance, & Potter, 2005) was used to diagnose the presence of chronic neuropathic pain at 3 and 6 months after surgery. The results showed that 8.7% and 5.2% of placebo-treated patients experienced chronic neuropathic pain 3 and 6 months after surgery, respectively. In contrast, not a single patient in the pregabalin-treated group was diagnosed with chronic neuropathic pain at either follow-up (Buvanendran, et al., 2010).

In another study, patients received either pregabalin (300 mg at 90 minutes preoperatively and 150 mg at 12 and 24 hours postoperatively) (n=20) or placebo (n=20) at corresponding times in a double-blinded manner while undergoing lumbar discectomy (Burke & Shorten, 2010). The primary outcome measure was a change in the intensity of pain as measured by a VAS from the preoperative assessment to 3-month follow-up. VAS pain scores were lower at 3 months (37.6 ± 19.6 mm) in treated patients compared to controls (25.3 ± 21.9 mm) (Burke & Shorten, 2010).

The final trial by Pesonen and colleagues randomly assigned 75 elderly patients (75 years of age or older) to receive either 150 mg of pregabalin before surgery and 75 mg of pregabalin BID for 5 postoperative days or placebo (Pesonen, et al., 2011). Elderly patients in this study who received pregabalin consumed fewer supplemental analgesics in the acute hospital period, and had lower confusion assessment scores on postoperative day 1. The incidence of pain during movement was significantly less in the pregabalin group 3 months after surgery.
However, unpublished results from industry posted on a major clinical trials registry (www.clinicaltrials.gov) has brought into question the evidence from these studies. There have been three phase III randomized placebo controlled multicenter trials conducted by Pfizer which assessed the efficacy of pregabalin in 3 different surgical models: 1) Patients undergoing total knee replacement (n=307) (ClinicalTrials.gov, 2011a) 2) Patients undergoing total abdominal hysterectomy (n=507) (ClinicalTrials.gov, 2011b) and 3) Patients undergoing primary inguinal hernia repair (n=425) (ClinicalTrials.gov, 2010) to decrease pain, reduce opioid consumption, improve rehabilitation and affect anxiety and depression. The results from the three unpublished studies failed to support the use of pregabalin for the prevention of chronic postsurgical pain. Other than a few isolated analyses which demonstrated that patients who received higher doses of pregabalin consumed less opioids acutely after surgery, no significant differences were found on chronic postsurgical pain outcomes and health related quality of life up to 6 months after surgery.

8.6 Conclusions

Chapter 4 highlighted the importance of continuing gabapentin into the postoperative time period in order to see the benefit with respect to decreasing opioid consumption and improving function in the acute postoperative time period. Furthermore, we found that maintaining gabapentin postoperatively lead to an increase in active assisted knee flexion to POD 3. In chapter 5 a single dose of gabapentin 600 mg was administered to examine the preemptive/preventive effects of gabapentin after total hip arthroplasty in a multimodal analgesic regimen, no difference was found in pain scores, opioid consumption, functional rehabilitation or the incidence of chronic pain 6 months following surgery. More
investigations are required to clarify the dosing regimens best suited to each surgical population preoperatively, in the immediate postoperative time period and into the discharge time period. It is also plausible that gabapentin might be more appropriate to be used in surgeries which elicit significant postoperative pain and often require relatively more opioid use to maintain pain scores in the mild range (i.e. <4/10). Given the documented postoperative opioid sparing effects of preemptive gabapentin use, patients presenting for surgery with longstanding opioid use due to previous chronic pain conditions or addition issues may also benefit from the perioperative administration medication.

Chapter 6 found that gabapentin did not reduce preoperative anxiety in a sample of patients that were not very anxious prior to hip arthroplasty. However, we followed those results by conducting a double blind randomized placebo controlled study (chapter 7) which examined the ability of gabapentin to reduce anxiety in a subpopulation of female patients with substantial preoperative anxiety. The results of that trial demonstrated that 1200 mg of gabapentin was efficacious in reducing preoperative anxiety when compared to placebo medication. Significant improvements in the methodology to date were the inclusion of an appropriately anxious population with an appropriate baseline assessment and the assessment of anxiety using several validated measures.

Given the findings presented in this dissertation, gabapentin continued into the postoperative period may benefit functional recovery during in-hospital physiotherapy. This beneficial effect should be weighed against the sedating effects of this medication which was demonstrated postoperatively in chapter 7 of this dissertation. The central mechanism of action of gabapentin within the CNS responsible for the sedation has not been well described, this common side effect may decrease the usefulness of gabapentin in the ambulatory/outpatient setting given that oversedation may prolong discharge and decrease patient flow in
the PACU. Given our findings and the literature to date, my recommendation is that gabapentin would be best utilized when given to elective in-patients for surgeries that are known to produce moderate to severe postoperative pain, patients that exhibit high levels of pre-operative anxiety, patients that have significant pre-operative pain conditions, and patients without renal compromise.
References


Appendix A – Pain and Anxiety Questionnaires

**Numeric Rating Scale (NRS) for Pain Intensity and Anxiety:** The NRS consists of a series of numbers ranging from 0 to 10 with endpoints representing the most extreme pain experiences (0 = ‘no pain’ and 10 = ‘worst possible pain’ for pain intensity and 0 = ‘no anxiety’, 10 = ‘extreme anxiety’ for anxiety). Patients choose the number that best corresponds to the intensity of their pain and to their anxiety. The NRS for pain has good reliability and validity and is sensitive to change following pharmacological intervention (Katz & Melzack, 1999).

**McGill Pain Questionnaire – Short Form-2 (SF-MPQ-2):** The SF-MPQ-2 (Dworkin, Turk, Revicki, Harding, Coyne, Peirce-Sandner, Bhagwat, Everton, Burke, Cowan, Farrar, Hertz, Max, Rappaport, & Melzack, 2009) is a 22-item, expanded and revised version of the SF-MPQ (Melzack, 1987) designed to measure the qualities of neuropathic and non-neuropathic pain. Exploratory and confirmatory factor analyses revealed the presence of the following four factors or subscales: (1) continuous pain, (2) intermittent pain, (3) neuropathic pain, and (4) affective pain descriptor. Preliminary analyses indicate that the SF-MPQ-2 has very good to excellent psychometric properties.

**Pain Catastrophizing Scale (PCS):** Pain catastrophizing has been defined as “an exaggerated negative mental set brought to bear during actual or anticipated painful experience”. (Sullivan, et al., 1995) The PCS (Sullivan, et al., 1995) consists of 13 items describing thoughts and feelings that individuals may experience when they are in pain. Each item is rated on a 5-point scale ranging from not at all (0) to all the time (4). The PCS yields
a total score and three subscale scores assessing (1) rumination, (2) magnification, and (3) helplessness. The PCS has good to excellent psychometric properties (Sullivan, et al., 1995).

**The State-Trait Anxiety Inventories (STAI):** The Speilberger State and Trait inventory (Spielberger, et al., 1983) consists of two self-report scales, one measuring state anxiety and the other measuring trait anxiety (Spielberger, et al., 1983). Each scale consists of 20 statements about how the respondent may feel, and they are asked to rate on a 4 point likert scale how strongly they agree (“very much so”) or disagree (“not at all”) with the item on the STAI-S, whereas the responses are “almost always” or “almost never” on the STAI-T. The S-Anxiety scale evaluates how respondents feel “right now, at this moment”, whereas the T-Anxiety scale evaluates how they feel “generally”. This scale has been used extensively in research and clinical practice, and has been shown to be valid and reliable (Spielberger, et al., 1983).

**Pain Anxiety Symptoms Scale-20 (PASS-20):** The PASS-20 (McCracken & Dhingra, 2002) is a shortened 20-item version of the original Pain Anxiety Symptoms Scale (McCracken, et al., 1992) designed to measure fear and anxiety responses specific to pain, including avoidance. The PASS-20 has four 5-item subscales, including (1) cognitive anxiety, (2) escape and avoidance, (3) fearful thinking, and (4) physiological anxiety. The PASS-20 has been shown to have good to excellent reliability and validity (McCracken & Dhingra, 2002).
Appendix B – Richmond Agitation Sedation Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ 4</td>
<td>Combative</td>
<td>Overtly combative or violent, immediate danger to staff</td>
</tr>
<tr>
<td>+ 3</td>
<td>Very agitated</td>
<td>Pulls on or removes tubes(s) or catheter(s) or has aggressive behaviour toward staff</td>
</tr>
<tr>
<td>+ 2</td>
<td>Agitated</td>
<td>Frequent nonpurposeful movement or patient-ventilator dyssynchrony</td>
</tr>
<tr>
<td>+ 1</td>
<td>Restless</td>
<td>Movements not aggressive or vigorous</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
<td></td>
</tr>
<tr>
<td>- 1</td>
<td>Drowsy</td>
<td>Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice</td>
</tr>
<tr>
<td>- 2</td>
<td>Light sedation</td>
<td>Briefly (less than 10 seconds) awakens with eye contact to voice</td>
</tr>
<tr>
<td>- 3</td>
<td>Moderate sedation</td>
<td>Any movement (but no eye contact) to voice</td>
</tr>
<tr>
<td>- 4</td>
<td>Deep sedation</td>
<td>No response to voice, but any movement to physical stimulation</td>
</tr>
<tr>
<td>- 5</td>
<td>Unarousable</td>
<td>No response to voice or physical stimulation</td>
</tr>
</tbody>
</table>

Procedure

1. Observe the patient. Is the patient alert and calm? (score 0)

Does the patient exhibit behaviour that is consistent with restlessness or agitation? (score + 1 to + 4 using the criteria listed above, under Description)

2. If the patient is not alert, in a loud speaking voice, state the patient’s name and direct the patient to open eyes and look at the speaker. Repeat once if necessary. Can prompt the patient to continue looking at speaker.

Patient demonstrates eye opening and eye contact that is sustained for more than 10 seconds (score – 1).

Patient demonstrates eye opening and eye contact, but not sustained for 10 seconds (score – 2).

Patient demonstrates any movement in response to voice, excluding eye contact (score – 3)

3. If the patient does not respond to voice, physically stimulate the patient by shaking shoulder. If there is no response to shaking shoulder, then rub sternum.

Patient demonstrates any movement to physical stimulation (score – 4)

Patient demonstrates no response to voice or physical stimulation (score – 5)
INTRODUCTION

You are being asked to participate in this study because you are scheduled for total knee arthroplasty and we are investigating the pain medication that you receive after your surgery. Postoperative pain relief is usually controlled with morphine using a pump that you can control yourself, sometimes called “PCA” (Patient Controlled Analgesia). Patients also receive a combination of tablets like an anti-inflammatory (Celecoxib), and opioids (strong pain killers), to get the best pain relief possible with the fewest side effects. Anti-Inflammatories are a type of pain medicine that reduces swelling (inflammation). We would like to see if using an additional painkiller called Gabapentin would provide you with better pain relief and improves your rehabilitation and your pain when you begin to walk.
**Why is this Study being done?**

Gabapentin, traditionally used for seizure disorders and nerve type pain has recently been shown to reduce the amount of morphine patients use after surgery and enhance rehabilitation in some orthopedic patients. This study will examine whether Gabapentin added to the pain management plan will decrease the need for a routine strong pain killer like morphine post operatively.

The purpose of this study is to determine the optimal dose for Gabapentin after your knee surgery, so that we can more effectively relieve postoperative pain after total knee replacement.

**What is involved in this study**

Each patient will receive celecoxib, Femoral and Sciatic Nerve Blocks, all which help with postoperative pain. One to two hours prior to surgery, you will be randomised to receive either Gabapentin 600mg or no Gabapentin (a placebo or sugar pill). You have an 80% chance of receiving the preoperative Gabapentin dose. The final step in preparation for surgery will be to have a spinal anesthetic for your knee replacement. After surgery, you will receive a Patient Controlled Analgesia device. In addition, after surgery, you will be once again randomized to receive Gabapentin 100mg TID (TID = 3 times/day), Gabapentin 200mg TID, Gabapentin 300mg TID or No Gabapentin TID (a placebo or sugar pills) for five days. We have chosen low/intermediate doses of gabapentin that have a good safety profile and should also provide you with good pain control. After surgery you have a 60% chance of once again receiving Gabapentin. Randomization in this study means that you will receive Gabapentin or not, based on chance, not by choice.

For your review, your pain management plan will be as follows:

All medications are either a capsule or tablet, and can be taken with a sip of water.

After Surgery you will receive:

200 mg of Celecoxib (an anti-inflammatory) twice a day for 5 days.
5 mg of Oxycontin (strong pain killer) every 8 hours for 5 days.
A pain pump (PCA) that will allow you to give yourself small doses of a strong pain killer (morphine), if you have pain. You will have the pain pump for the first 48 hours after your surgery. You cannot use too much of this, the PCA machine will not let you.

You will be randomly assigned to receive the placebo, Gabapentin 100mg 3 times a day for 5 days, Gabapentin 200mg 3 times a day for 5 days or Gabapentin 300mg 3 times a day for 5 days.

*NOTE: If you are determined by the pain experts performing this study to have allergies to the above medications, or other conditions that prevent the use of any of the above medications you will be excluded from the study.

Part of this research will involve the collection of information from you that describes any pain or discomfort that you experience after surgery. After your surgery, you will be asked about how much pain you have by the nursing staff. In order to address these issues, you are asked to provide the following information at various intervals during your hospital stay:

Pain intensity – using a Visual Analogue Scale (VAS) where 0=no pain and 100=Terrible Pain will be recorded every 4 hours for 72 hours, then every 8 hours thereafter until the completion of the study. You will also be asked to rate your pain after two rehabilitation measures on Postoperative day 3 and Postoperative day 5. You will also be asked if you are feeling nauseated, feel like vomiting, or feel drowsy.

After Total Knee Arthroplasty, it is important that all patients receive a standardized rehabilitation protocol. At the Orthopedic and Arthritic Institute, the Primary Knee Replacement Care Pathway is accompanied by a standardized rehabilitation treatment protocol. While you are in hospital, you will meet your physiotherapist who will put you through a series of knee exercises. The physiotherapist will record how much movement you can perform with your knee every day that you are in hospital. On postoperative day 3 and day 5 you will, in addition to your daily knee exercises be asked to perform a walking test to the best of your ability. You will be timed, your
physiotherapist will ask you to stand from a chair and walk 3 meters at a comfortable safe pace. You will then turn and walk back to the chair, then sit down. In order that you be familiar with that test we will perform that exercise before your operation so that we can obtain a baseline score. At the completion of the walking test, you will also be asked to provide a final pain assessment of how painful the walking test was.

HOW MANY PEOPLE WILL BE INVOLVED AND FOR HOW LONG?
250 people will be needed to complete the study. They will be involved in the study for the first 5 days after surgery.

What are the risks of the study?
The risks of side effects by being in the study are no more or less than you would be at risk for using standard pain treatment. The most common side effects of Gabapentin are feeling drowsy (20%), dizziness (18%), difficulty in co-ordinating muscle movement (13%) and tiredness (11%). Because Gabapentin is usually a part of pain treatment at Sunnybrook, the risk of side effects is no more or less than you would be at risk for using standard pain treatment. During the study a pain doctor, pain nurse practitioner, and a pharmacist will be carefully monitoring you to make sure you are safe and comfortable.

WHAT OTHER OPTIONS ARE THERE?
Joining this study is entirely your choice. You may choose to not be involved and receive the usual treatment which may include some of the same drugs. At any time during the study if you feel your pain is not well controlled or you have too many side effects, or you change your mind, you can withdraw from the study and the Pain Management Team will do everything they can to best manage your pain and side effects. The doctor may also discontinue your participation in this study without your consent should any unexpected event occur during the study or if you have difficulty doing what is necessary to complete the study.
Are there any benefits to joining this study?

You may or may not benefit directly from this study; however, the information that is gathered from this study will allow the multidisciplinary team to optimize postoperative pain and assess Gabapentin’s effect on rehabilitation outcomes and movement associated pain after Total Knee Arthroplasty.

What about Confidentiality?

Every effort will be made to keep your personal information confidential. All records of your involvement in this research study will be stored in a secure space. Only a case number and your initials will identify you. You will not be identified in any publication of the results. Confidentiality will be respected as no information that discloses your identity will be released or published without consent unless required by law. Only the investigators and the Research Ethics Board who oversees the ethical conduct of this study in the hospital, will be allowed to view your personal information.

What are your rights as a participant?

Your participation in this study is entirely voluntary. You may choose to not take part or may leave the study at any time. Deciding to not take part, or deciding to leave the study later will not result in any penalty or any loss of benefits to which you are entitled. By signing this consent form, you do not waive any of your legal rights nor do you release the investigators from their legal and professional responsibilities. We will tell you about new information that may affect your health, welfare, or willingness to stay in the study.

Who do you call if you have questions?

You may ask questions about this form or the study now or at any time during the study. If you have problems, or have questions about the research or a problem
during the study, you may call Dr. Hance Clarke at 416 480 6100 x 1718 or Dr. Joseph Kay, Staff Anesthesiologist at 416-480-4798.

If you have questions about your rights as a participant in this study, please contact the Office of Research Administration at Sunnybrook & Women’s College Health Sciences Centre at 416-480-4276.

Statement of Study Subject and Signature:

- I voluntarily agree to participate in this study.
- I understand that the study sponsor may stop the study at any time. If this happens I will no longer receive the planned evaluations.
- I understand that I will receive a signed and dated copy of this consent form.
- I understand that I may withdraw my consent at any time.
- I have had a chance to ask questions and understand the answers given to all of my questions.
- I have read and understand the above information,
- I have been given the chance to ask questions, and these questions have been answered to my satisfaction,

  

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STATEMENT OF INVESTIGATOR OR AUTHORIZED PERSONNEL:

I certify that I have explained to the above individual the nature and purpose of the study, potential benefits, and possible risks associated with participation in this study to the subject and/or the person authorized to consent for this subject. I have answered any questions that have been raised and have witnessed the above signature. I have explained the above to the subject and/or person authorized to consent for this subject on the date stated on this consent form. I am qualified to perform this role.

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<td>Signature of Study Coordinator</td>
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Evaluation of Gabapentin as a Preemptive Analgesic for Patients Undergoing Total Hip Arthroplasty.

Principal Investigator: Dr. Hance Clarke  
Department of Anaesthesia  
Sunnybrook & Women’s College Health Sciences Centre  
2075 Bayview Avenue  
Toronto, ON M4N 3M5

Emergency Contact Information: Dr. Joseph Kay  416 480 4798 pager: 416 563 6987  
Dr. Hance Clarke pager: 416 370 7669

Study Sponsor: Physicians Services Incorporated Foundation

INTRODUCTION

You are being asked to participate in this study because you are scheduled for hip arthroplasty and we are investigating the pain medication that you will receive for your surgery. Postoperative pain relief is usually controlled with morphine (strong pain killer) using a pump that you can control yourself, sometimes called “PCA” (Patient Controlled Analgesia). Patients also receive a combination of tablets like acetaminophen (Tylenol), an anti-inflammatory (Celecoxib), and opioids (strong pain killers), to get the best pain relief possible with the fewest side effects. Anti-Inflammatories are a type of pain medicine that reduces swelling (inflammation). We would like to see if using an additional painkiller called Gabapentin either before or after surgery, improves your pain for the first 48 hours after surgery.

Why is this Study being done?

Gabapentin, traditionally used for seizure disorders and nerve type pain has recently been shown to reduce the amount of morphine patients use after surgery and decrease the amount of pain they report. This study will examine when the best time to give Gabapentin would be. We will look at Gabapentin given prior to surgery and
immediately after surgery to determine which regimen produces the greatest decrease in the need for a routine strong pain killer like morphine post operatively.

The purpose of this study is to determine the optimal timing for Gabapentin while in hospital undergoing your hip surgery, so that we can more effectively relieve postoperative pain after total hip replacement. Recent studies have shown that Gabapentin can provide pain relief and reduce the amount of strong pain killers used (i.e. morphine). There is also evidence that Gabapentin reduces pain associated with movement which is a critical component of your recovery. Gabapentin is currently given to more than 80% of all patients having their hips replaced at the Orthopedic and Arthritic Institute.

**What is involved in this study?**

All patients who participate in this study will be randomized to one of t treatment arms. Each patient will receive acetaminophen and celecoxib, prior to surgery, all which help with postoperative pain. One to two hours prior to surgery, you will be randomized to receive either Gabapentin 600 mg or no Gabapentin (a placebo or sugar pill). You have a 33% chance of receiving the preoperative Gabapentin dose. The final step in preparation for surgery will be to have a spinal anesthetic for your hip replacement. After surgery, you will receive a Patient Controlled Analgesia device. In addition, after surgery, you will be once again randomized to receive Gabapentin 600 mg or no Gabapentin (a placebo or sugar pill). After surgery, you again have a 33% chance of receiving Gabapentin. Overall you have a 66% chance of receiving Gabapentin during this study, you will not receive it more than once. Randomization in this study means that you will receive Gabapentin or not, based on chance, not by choice.

For your review, your pain management plan will be as follows:

All medications are either a capsule or tablet, and can be taken with a sip of water.

Prior to Surgery you will receive:
1 g of Acetaminophen
Celecoxib 400 mg

You will be randomly assigned to receive Gabapentin 600 mg or placebo.

After Surgery you will receive:
1 g of Acetaminophen (Tylenol) tablets every six hours for 3 days.
200 mg of Celecoxib (an anti-inflammatory) twice a day for 3 days.

You will be randomly assigned to receive Gabapentin 600 mg or placebo.

A pain pump (PCA) that will allow you to give yourself small doses of a strong pain killer (morphine), if you have pain. You will have the pain pump for the first 48 hours after your surgery. You cannot use too much of this, the PCA machine will not let you.

*NOTE: If you are determined by the pain experts performing this study to have allergies to the above medications, or other conditions that prevent the use of any of the above medications you will be excluded from the study.

Part of this research will involve the collection of information from you that describes any pain or discomfort that you experience after surgery. After your surgery, you will be asked about how much pain you have by the nursing staff. In order to address these issues, you are asked to provide the following information at various intervals during your hospital stay:

Pain intensity – using a Visual Analogue Scale (VAS) where 0=no pain and 100=Terrible Pain will be recorded every 4 hours for 48 hours until the completion of the study.

You will also be asked if you are feeling nauseated, feel like vomiting, or feel drowsy.

Some cox-2 inhibitors have been recently removed from the market, Celecoxib (or Celebrex) has continued to be available for presurgical and postsurgical use and is considered to be low risk in terms of side effects and effective in treating perioperative pain.
HOW MANY PEOPLE WILL BE INVOLVED AND FOR HOW LONG?

90 people will be needed to complete the study. They will be involved in the study for the first 48 hours after surgery. We will also contact you 6 to 8 months after your surgery to ask you how you are doing and administer a 15 minute telephone questionnaire about any pain that you may be experiencing.

What are the risks of the study?

The risks of side effects by being in the study are no more or less than you would be at risk for using standard pain treatment. The most common side effects of Gabapentin are feeling drowsy (20%), dizziness (18%), difficulty in co-ordinating muscle movement (13%) and tiredness (11%). Because Gabapentin is usually a part of pain treatment at Sunnybrook, the risk of side effects is no more or less than you would be at risk for using standard pain treatment. During the study a pain doctor, pain nurse practitioner, and a pharmacist will be carefully monitoring you to make sure you are safe and comfortable.

WHAT OTHER OPTIONS ARE THERE?

Joining this study is entirely your choice. You may choose to not be involved and receive the usual treatment which may include some of the same drugs. At any time during the study if you feel your pain is not well controlled or you have too many side effects, or you change your mind, you can withdraw from the study and the Pain Management Team will do everything they can to best manage your pain and side effects. The doctor may also discontinue your participation in this study without your consent should any unexpected event occur during the study or if you have difficulty doing what is necessary to complete the study.

Are there any benefits to joining this study?

You may or may not benefit from your participation in this study; however, the information that is gathered from this study will allow the multidisciplinary team to
optimize postoperative pain and determine the best time to administer Gabapentin in patients undergoing Total Hip Arthroplasty.

**What about Confidentiality?**

Every effort will be made to keep your personal information confidential. All records of your involvement in this research study will be stored in a secure space. Only a case number and your initials will identify you. You will not be identified in any publication of the results. Confidentiality will be respected as no information that discloses your identity will be released or published without consent unless required by law. Only the investigators and the Research Ethics Board who oversees the ethical conduct of this study in the hospital, will be allowed to view your personal information. Representatives of Health Canada may review the medical records of any study subject in order to ensure that the study was carried out as planned.

**What are your rights as a participant?**

Your participation in this study is entirely voluntary. You may choose to not take part or may leave the study at any time. Deciding to not take part, or deciding to leave the study later will not result in any penalty or any loss of benefits to which you are entitled. By signing this consent form, you do not waive any of your legal rights nor do you release the investigators from their legal and professional responsibilities.

We will tell you about new information that may affect your health, welfare, or willingness to stay in the study.

**Who do you call if you have questions?**

You may ask questions about this form or the study now or at any time during the study. If you have problems, or have questions about the research or a problem during the study, you may call Beth Goudie (Study Co-ordinator) at 416-967-8587, Dr. Joseph Kay, Staff Anesthesiologist at 416-480-4798, or page Dr. Hance Clarke at 416-370-7669.
If you have questions about your rights as a participant in this study, please contact the Office of Research Administration at Sunnybrook & Women’s College Health Sciences Centre at 416-480-4276.

Statement of Study Subject and Signature:

- I voluntarily agree to participate in this study.
- I understand that the study sponsor may stop the study at any time. If this happens I will no longer receive the planned evaluations.
- I understand that I will receive a signed and dated copy of this consent form.
- I understand that I may withdraw my consent at any time.
- I have had a chance to ask questions and understand the answers given to all of my questions.
- I have read and understand the above information,
- I have been given the chance to ask questions, and these questions have been answered to my satisfaction,

 abaixo:

Signature of Subject/Participant  Printed Name of Subject/Participant  Date

STATEMENT OF INVESTIGATOR OR AUTHORIZED PERSONNEL:

I certify that I have explained to the above individual the nature and purpose of the study, potential benefits, and possible risks associated with participation in this study to the subject and/or the person authorized to consent for this subject. I have answered any questions that have been raised and have witnessed the above signature. I have explained the above to the subject and/or person authorized to consent for this subject on the date stated on this consent form. I am qualified to perform this role.

Signature of Witness  Printed Name of Witness  Date

Signature of Investigator  Printed Name of Investigator  Date

Signature of Study Coordinator  Printed Name of Study Coordinator  Date
CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY
Study Title: Gabapentin As A Preoperative Anxiolytic Agent: A Randomized, Double-Blind, Placebo-Controlled Trial

Principal Investigator: Dr. Hance Clarke
Phone: (416) 340-4800 - ext. 6649

Co-Investigators: Dr. Rita Katznelson, Dr. Raynauld Ko, Dr. Joel Katz
Dr. Beverly Orser

24 Hour Pager Phone Number: (416) 719-2726

Introduction:

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purposes, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study doctor or study personnel to explain any words you don’t understand before signing this consent form. Make sure all your questions have been answered to your satisfaction before signing this document.

Purpose:

You have been asked to participate in a study, which is designed to evaluate the effectiveness of a medication called Gabapentin and whether Gabapentin decreases anxiety before surgery. Gabapentin is approved by Health Canada for the treatment of epilepsy. You are eligible for this study because you are female, between the ages of 18 and 50 and are scheduled to undergo surgery at our hospital.
We will be assessing the anxiety that you may experience before your surgery using various questionnaires. We will be collecting one blood sample following induction of anesthesia (you will be asleep) to measure blood levels of steroid metabolites (specific products that are released into the blood after ingestion of the medication) that may be related to the effects of Gabapentin that help to decrease your anxiety. We are conducting this study at University Health Network, Toronto General Hospital and 50 subjects will participate. If you are deemed not to have sufficient preoperative anxiety, you will not be eligible to participate in this trial. The focus of the study is to determine whether gabapentin can decrease preoperative anxiety, therefore a level of preoperative sufficient anxiety is needed in order to test this theory.

**Procedures:**

If you agree to participate in this study and upon signing this Consent Form you will first be asked to complete a brief questionnaire on how anxious you are using a numeric rating scale with a rating of 0 to 10. You will then be required asked to complete questionnaires the morning of your surgery. Answering the questionnaires will take about 10 – 15 minutes to complete. The questionnaires will include questions regarding how you are feeling in general. All of the questionnaires you will be asked to complete are commonly used and they are designed to measure anxiety and how you cope with negative thoughts that are associated with your surgery; how you deal with stressful life experiences; and how you have been able to cope with anxiety.

You will receive the usual standard of care. In addition, You will be randomly assigned to receive either Gabapentin 1200 mg or a placebo (looks like gabapentin, but contains no active ingredient). Random assignment means that your chances of receiving the drug Gabapentin or placebo is 50%. Placebo is a pill that does not contain any drug. You and the study personnel will not know if you will get placebo or drug, however, the study personnel can get this information quickly, from our pharmacy, if it is needed. Because this is a research study, study medication will be given to you only during your participation in the study.
Gabapentin is approved by Health Canada for the treatment of epilepsy. In other studies, Gabapentin has been shown to be effective for reducing anxiety before surgery, pain after surgery, the amount of pain medication required and improving your physical performance after surgery. However, you understand that this drug is not approved for the treatment of anxiety before surgery. We are studying this potential benefit with this trial.

On the day of your surgery you will receive either Gabapentin 1200 mg or you will receive the placebo 2.5 hours prior before to your surgery. Two hours after you take the medication you will be given the questionnaires to complete again.

Upon completion of this second set of questionnaires your participation in this study will be considered complete, after a the only other step will be the blood sample has been collected once you have been put to sleep for your operation. The blood sample will be marked with a random number assigned to you to ensure your privacy. We will be reviewing your health care records and document any side effects (unwanted effects or health problems) you experience, whether related to the study drug or not.

**RISKS AND BENEFITS**

Most common side effects of Gabapentin are drowsiness (20%), dizziness (18%), difficulty in coordinating muscle movement (13%), tiredness (11%). Less common side effects (1% to 3%) include nausea, vomiting, itchiness, dry mouth, constipation, and nervousness. You will be anesthetized at the time of blood draw and feel no discomfort, however there remains a small risk that you may develop a bruise or an infection at the blood draw site.

There are no known personal benefits associated with taking part in this research study. Information learned from this study may benefit others undergoing surgery in the future, and may further the understanding of medication requirements for those experiencing anxiety. This study may also help us develop tools or interventions aimed at reducing anxiety prior to surgery.

**BENEFITS:**

You may or may not receive any direct benefit from being in this study. Information learned from this study may help other people with your condition in the future.
IN CASE YOU ARE HARMED IN THE STUDY

If you become ill, injured or harmed as a result of taking part in this study, you will receive care. The reasonable costs of such care will be covered for any injury, illness or harm that is directly a result of being in this study. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors or involved institutions from their legal and professional responsibilities. You do not give up any of your legal rights by signing this consent form.

CONFIDENTIALITY:

Personal Health Information

If you agree to join this study, the study doctor and his/her study team will look at your personal health information and collect only the information they need for the study. Personal health information is any information that could be used to identify you and includes your:

- name,
- address,
- date of birth,
- new or existing medical records, that includes types, dates and results of medical tests or procedures.

The information that is collected for the study will be kept in a locked and secure area by the study doctor for 25 years. Only the study team, Health Canada (or other regulatory bodies (groups of people who oversee research studies) outside of Canada, such as the United States Food and Drug Administration and the UHN REB will be allowed to look at your records to check that the information collected for the study is correct and to make sure the study followed proper laws and guidelines. Your participation in this study also may be recorded in your medical record at this hospital.

Study Information that Does Not Identify You

All information collected during this study, including your personal health information, will be kept confidential and will not be shared with anyone outside the study unless required by law.

You will not be named in any reports, publications, or presentations that may come from this
If you decide to leave the study, the information about you that was collected before you left the study will still be used. No new information will be collected without your permission.

**EXPENSES ASSOCIATED WITH PARTICIPATING IN THE STUDY**

You will not have to pay for any of the procedures or study drug (gabapentin) involved with this study. You will not be reimbursed for transportation, meals, time, inconvenience, etc.

All information obtained during the study will be held in strict confidence and none of the information that we collect will be transferred out of the University Health Network. The investigators, Drs. Hance Clarke, Rita Katznelson, Raynauld Ko, Beverley Orser and Joel Katz, the University Health Network Research Ethics Board, and research personnel working on this project will be the only ones who will have access to your hospital medical records containing your personal health information. You will be identified by a study number and initials only. No names or identifying information will be used in any publication or presentation.

If you become ill or physically injured as a result of participation in this study, medical treatment will be provided. The reasonable costs will be covered by your health insurance.

**PARTICIPATION:**

Your participation in the study is voluntary. You may withdraw from the study at any time, or to be in the study now and then change your mind later, and you can also choose not to answer any questions that you do not feel comfortable answering. You may leave the study at any time without affecting your medical care. You may refuse to answer any question you do not want to answer, or not answer an interview question by saying “pass”. We will give you new information that is learned during the study that might affect your decision to stay in the study. This will not affect your medical care.

**QUESTIONS:**

If you have any question related to this study please call the Principal Investigator, Dr. Hance Clarke, at (416) 340-4800 ext. 6649 or you may contact the study coordinator, Eileen Halket, RN at (416) 340-4800 ext. 4251.
If you have any questions about your rights as a research participant, please call Dr. R. Heslegrave, Chair of the University Health Network Research Ethics Board at (416) 340-4557. This person is not involved with the research project in any way and calling him will not affect your participation in the study.

In no way does signing this consent form waive your legal rights nor does it relieve your doctors or UHN from their legal and professional responsibilities.

**CONSENT:**

I have had the opportunity to discuss this study and my questions have been answered to my satisfaction. I consent to participate in the study with the understanding that I may withdraw at any time without affecting my medical care. I will receive a signed copy of this consent form. I voluntarily consent to take part in this study.

_________________________________  __________________________________________
Study Participant (Please Print)  Study Participant’s Signature

_________________________________
Date

I confirm that I have explained the nature and purpose of the study to the subject named above. I have answered all questions.

_________________________________  __________________________________________
Name of Person Obtaining Consent  Signature

_________________________________
Date
Author Contributions

Chapter 4: Gabapentin decreases morphine consumption and improves functional recovery following total knee arthroplasty.

Drs. Joseph Kay, Ian Gilron and Joel Katz provided input into the study design. Sara Pereira was the acute pain nurse involved in the care of the patients in the protocol. Deborah Kennedy was a physiotherapist involved in the postoperative care of the patients in the protocol. Jeffrey Gollish is an orthopedic surgeon at the Holland Orthopedic and Arthritic Centre that provided institutional and administrative support for this study.

Chapter 5: Gabapentin added to a multimodal regimen with spinal anesthesia does not reduce acute pain, opioid consumption, or chronic pain up to six months after total hip arthroplasty.

Drs Joseph Kay and Joel Katz were integral with respect to study design. Sara Pereira was the acute pain nurse involved in the care of the patients in the protocol. Deborah Kennedy and Jeffrey Andrion were physiotherapists involved in the postoperative care of the patients in the protocol. Dr. Nicholas Mitsakakis was the statistician responsible for the statistical analyses. Jeffrey Gollish is an orthopedic surgeon at the Holland Orthopedic and Arthritic Centre that provided institutional and administrative support for this study.

Chapter 6: Gabapentin does not reduce preoperative anxiety when given prior to total hip arthroplasty.

Drs. Joseph Kay, Beverly Orser and Joel Katz were involved with the creation of the study question and project. Dr. Nicholas Mitsakakis was the statistician responsible for the statistical analyses. Jeffrey Gollish is an orthopedic surgeon at the Holland Orthopedic and Arthritic Centre that provided institutional and administrative support for this study.
Chapter 7: Gabapentin reduces preoperative anxiety and pain catastrophizing in highly anxious patients prior to major surgery.

Drs. Rita Katzenelson, Beverley Orser and Joel Katz were integral with respect to study design. Dr. Kyle Kirkham was a colleague responsible for recruitment and patient flow at the Toronto General Hospital. Dr. Nicholas Mitsakakis was the statistician responsible for all statistical analyses performed with respect to the study. Drs. Raynauld Ko, Martin Ma and Adam Snyman were responsible for clinical care issues that arose with patients in this study and approved the final manuscript prior to the acceptance for publication in the May 2013 edition on the Canadian Journal of Anesthesia.
Copyright Acknowledgements

The following manuscripts, which are located in Chapters 4, 5, 6 and 7 of this dissertation have been published. Permission to reproduce the published manuscripts was granted for use in this dissertation:


Hance A. Clarke, Sara Pereira, Deborah Kennedy, Jeffrey Andrion, Nicholas Mitsakakis, Jeffrey Gollish, Joel Katz, Joseph Kay. Gabapentin added to a multimodal regimen with spinal anesthesia does not reduce acute pain, opioid consumption or chronic pain up to six months after total hip arthroplasty. *Acta Anesthesiologica Scandinavica*, Sept 2009, 53 (8):1073-83.


Hance A. Clarke, Kyle Kirkham, Beverley A. Orser, Robert Bonin, Nicholas Mitsakakis, Rita Katznelson, Raynauld Ko, Martin Ma, and Joel Katz. Gabapentin reduces preoperative anxiety and pain catastrophizing prior to major surgery in highly anxious patients: a blinded

Selected passages from the following manuscripts were reproduced with permission in Chapters 2, and 8.
