OPTIMIZING CHRONIC PAIN AND DISABILITY MANAGEMENT

ISSUES RELATED TO OPTIMIZING CHRONIC NON-CANCER PAIN AND DISABILITY MANAGEMENT

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ABSTRACT

Chronic non-cancer pain (CNCP) is a complex phenomenon that affects multiple dimensions of daily life. Optimal therapies for managing CNCP must, then, demonstrate clinically important benefits that go beyond reductions in pain and adverse events. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has recommended that clinical trialists who are evaluating treatments for chronic pain consider reporting treatment effects across nine patient-important outcome domains. This thesis begins with an investigation of the extent to which clinical trials evaluating the effects of opioids for CNCP report IMMPACT-recommended core outcome domains. Further, it explores optimal therapeutic strategies for specific CNCP conditions; specifically, it features a systematic review of randomized controlled trials of all pharmacological and non-pharmacological therapies for central post-stroke pain, as well as a plan for a network meta-analysis of all therapies for all chronic neuropathic pain syndromes. Chronic pain is also a common reason for disability, and this thesis concludes with a retrospective cohort study focused on identifying predictors of claim duration following acceptance for disability benefits among Canadian workers.

DEDICATION

To RK, my sun on cloudy days.

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TABLE OF CONTENTS

LIST OF TABLES

Chapter 2

Chapter 3

Chapter 5

LIST OF FIGURES

Chapter 3

Chapter 5

DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis is a "sandwich" thesis, which combines four individual studies prepared for publication in peer-reviewed journals. At the time of writing this thesis, the first two studies have been published, the third has been accepted for publication, and the fourth has not been submitted. I am the first author for all studies. With guidance from my supervisor, Dr. Jason W. Busse, my contributions to all the papers included in this dissertation are as follows: developing the research question; writing the protocol and statistical analysis plan; data collection and management; conducting the statistical analyses; designing the figures; writing all the manuscripts; and, where applicable, submitting the manuscripts and responding to reviewers' comments. My co-authors contributed in acquiring, managing and analyzing data, and preparing the manuscripts for publication. The work in this thesis was conducted between September 2013 and August 2015.

CHAPTER 1

INTRODUCTION

Chronic non-cancer pain (CNCP) comprises any painful condition that persists for at least three months, and is not associated with malignancy. CNCP is a major public health issue, with reports estimating up to 55% of adults may suffer from CNCP.[1] Prevalence rates are higher among women, and older individuals.[2-4] CNCP has a marked negative impact on quality of life and physical functioning.[5-10]

Several options for managing chronic pain exist, including pharmacological and non-pharmacological interventions. Clinical trialists evaluating these strategies must, however, attend to the challenge that chronic pain is a complex phenomenon affecting multiple dimensions of life, and which commonly presents with multiple co-morbidities. In response, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) – a consortium of academic institutions, industry partners, and government agencies – was established. Its objective is to facilitate improved design, execution, and conduct of chronic pain clinical trials by publishing recommendations about clinical trial methodology. One of IMMPACT's first initiatives was to recommend standardized measurement and reporting of treatment effects across nine

patient-important outcome domains: (1) pain; (2) physical functioning; (3) emotional functioning; (4) participant ratings of global improvement and satisfaction with treatment; (5) symptoms and adverse events; (6) participant disposition; (7) interpersonal functioning; (8) role functioning; and, (9) sleep and fatigue.[11,12] **Chapter 2** of this thesis presents the results of a study in which we evaluated the extent to which randomized controlled trials that tested the use of opioids for management of CNCP evaluated and reported treatment effects across the IMMPACT-recommended core outcome domains. This was the first study of its kind, and set out to challenge anecdotal evidence suggesting that outcome reporting has improved following publication of IMMPACT's recommendations.[13] In this chapter, we also discuss the merits and challenges of the IMMPACT approach.

While CNCP conditions can be debilitating, few are as incapacitating as central post-stroke pain (CPSP) – a chronic neuropathic disorder that may affect up to 25% of individuals who suffer a stroke.[14] Individuals with CPSP commonly experience sensory abnormalities, including increased tactile and thermal sensitivities, which significantly impact their quality of life.[15-17] Management of CPSP is of special interest to McMaster University, where the Michael G. DeGroote Institute for Pain Research and Care was established to specifically advance research on CPSP. **Chapter 3** presents the results of a systematic review of randomized controlled trials of all therapies (pharmacological and

non-pharmacological) for the management of individuals with CPSP. Our study addressed the limitations of prior reviews to optimally inform management of CPSP. This was also the first published systematic review to measure and report treatment effects across the nine IMMPACT-recommended core outcome domains. We used state-of-the-art methodology, such as the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rate our certainty in the evidence. We contextualized our findings by comparing them with clinical practice guidelines by three major professional groups – International Association for the Study of Pain Neuropathic Pain Special Interest Group (IASP NeuPSIG), the European Federation of Neurological Societies (EFNS), and the Canadian Pain Society (CPS).

We build upon the results in the previous chapter by presenting, in **Chapter 4**, a protocol for a systematic review and network meta-analysis of randomized controlled trials of all therapies for chronic neuropathic pain. Network meta-analysis is an increasingly popular statistical method that facilitates estimation of relative benefits and harms of treatments that have not been tested directly against each other in clinical studies. For CNCP especially, not only are there several interventions available, but treatments are also infrequently compared against one another. For instance, authors of a systematic review found that, among 131 randomized controlled trials (RCTs) addressing 54 different pharmacological options for peripheral neuropathic pain, only 35 trials (27%)

compared drugs directly against each other.[18] This paucity of direct evidence makes it difficult to estimate treatments' relative benefits and harms, thereby decreasing the utility of the published evidence to stakeholders.

Disability secondary to CNCP is also associated with significant lost work and decreased work effectiveness.[19-22] In 2014, full-time employees in Canada took an average of 7.4 sick days,[23] while United Kingdom workers lost 131 million days due to sickness absence in 2013.[24] Lost time off work, irrespective of the underlying disability or illness, is associated with substantial financial implications; researchers estimate poor health annually costs the United States economy, for instance, over $500 billion, of which sickness absence accounts for over $225 billion.[25] Absenteeism rates are observed to be highest among women, and individuals working in the health care and social assistance sector. With the global population rapidly ageing,[26] and a greater number of older workers taking sick leave versus younger workers,[27] there is an urgent need to address the increasing burden of managing employee absence.

Efforts to manage sick workers, optimize recovery, and facilitate sustained return to work are of interest to a variety of stakeholders. Disability insurers, in particular, are interested in developing greater insights into factors, especially those that are modifiable, which are associated with claim duration, so they can optimize their case management policies and processes to reduce overall

claim durations. Members of our research group previously worked with a large Canadian private disability insurer to identify several demographic, clinical, and administrative factors associated with benefits duration.[28] For this thesis, I worked with another large Canadian private disability insurer to confirm our group's previous findings, and test additional factors that we hypothesized could be predictive of claim duration. **Chapter 5** presents the results of this study in which we analyzed over seven years of data for approximately 100,000 claimants. This was the largest study of its kind to explore predictors of disability benefits claim duration.

My thesis ends with **Chapter 6**, which summarizes the most important findings, addresses limitations, and discusses future directions from the body of work I describe above.

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CHAPTER 2

At the time of writing this thesis, this chapter has been published in a peer-reviewed scientific journal, as follows:

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Reporting of IMMPACT-recommended core outcome domains among trials assessing opioids for chronic non-cancer pain

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ABSTRACT

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has recommended that trialists evaluating treatments for chronic pain should consider reporting nine patient-important outcome domains. We examined the extent to which clinical trials evaluating the effect of opioids for chronic non-cancer pain (CNCP) report outcome domains recommended by IMMPACT. We systematically searched electronic databases for English-language studies that randomized patients with CNCP to receive an opioid or a non-opioid control. In duplicate and independently, reviewers established the eligibility of each identified study, and recorded all reported outcome domains from eligible trials. We conducted a priori regression analyses to explore factors that may be associated with IMMPACT recommended outcome domains. Among 156 eligible trials, reporting of IMMPACT recommended outcome domains was highly variable, ranging from 99% for pain to 7% for interpersonal functioning. Recently published trials were more likely to report the effect of treatment on physical functioning, emotional functioning, role functioning, sleep and fatigue, and participant disposition. Trials for which the corresponding author was from North America were more likely to report treatment effects on physical functioning, and participant ratings of improvement and satisfaction with treatment. Trials published in higher impact journals were more likely to report treatment effects on emotional function,

but less likely to report participant ratings of improvement and satisfaction with treatment. Most IMMPACT domains showed an increased rate of reporting over time, although many patient-important outcome domains remained unreported by over half of all trials evaluating the effects of opioids for CNCP.

INTRODUCTION

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) first convened in 2002 to establish a standard set of patient-important outcome domains to guide the reporting of RCTs evaluating therapies for chronic pain.[17] In a 2003 paper, this group, which includes representatives from the academic, governmental, and pharmaceutical communities, recommended that researchers report the following six core outcome domains in chronic pain clinical trials: (1) pain; (2) physical functioning; (3) emotional functioning; (4) participant ratings of global improvement and satisfaction with treatment; (5) symptoms and adverse events; and, (6) participation disposition. In a 2008 publication, after conducting focus groups and surveys of individuals with chronic pain, IMMPACT recommended an additional three core outcome domains: (7) role functioning; (8) interpersonal functioning; and (9) sleep and fatigue.[18]

Establishing a standard set of outcome domains among chronic pain clinical trials has several merits. First, it encourages trialists to consider chronic pain as a complex phenomenon that affects patients across multiple dimensions.[2; 3; 7; 11; 12; 19; 20] Second, it protects against selective outcome reporting bias, which is a common issue across the medical literature.[4; 5] Third, it facilitates the conduct of systematic reviews and meta-analyses, which allow researchers

to generate more precise estimates of treatment effects by pooling common outcome data from individual trials.[10]

While there have been anecdotal claims of improved outcome reporting following publication of IMMPACT's recommendations,[16] there is no empirical evidence to support these assertions. Hence, we explored this issue among clinical trials evaluating the effectiveness of opioids for chronic non-cancer pain.

METHODS

Literature search

We searched for relevant studies, in any language, by tailored searches of AMED, CINAHL, CENTRAL, EMBASE, HealthSTAR, MEDLINE, and PsycINFO, from the inception of each database through March 2, 2012. An experienced academic librarian (RC) collaborated in the development of the search strategy for each electronic database.

Eligibility criteria

We included English-language studies if they randomly allocated patients with chronic non-cancer pain to opioid therapy or any non-opioid control group.

Study selection and data abstraction

Teams of reviewers worked independently and in duplicate to determine eligibility status of all identified citations, first by screening the titles and abstracts, then by reviewing the full texts of all potential eligible articles. Two reviewers (AM and LS) used a pilot-tested, standardized form to extract information, including details on all reported IMMPACT core outcome domains, from each eligible study. We also examined details about the study participants, interventions, and authors to assess whether multiple eligible articles resulted from the same trial. A third reviewer (LCL) independently confirmed data extraction from every 10th article for quality assurance

purposes. Reviewers resolved any disagreements by discussion, or with the help of an adjudicator (JWB).

Statistical analyses

We measured agreement at the stage of full-text review and interpreted the chance-independent agreement (Φ) for selection of eligible studies.[8] Values of 0 to 0.20 represented slight agreement, 0.21 to 0.40 represented fair agreement, 0.41 to 0.60 represented moderate agreement, 0.61 to 0.80 represented substantial agreement and greater than 0.80 represented almost perfect agreement.[13] We summarized the data using the mean and standard deviation (SD) for continuous variables that were normally distributed, the median and interquartile range (IQR) for continuous variables that were not normally distributed, and proportions for categorical variables.

We conducted adjusted logistic regression analyses and hypothesized, *a priori*, the following associations with higher rates of reporting IMMPACT-recommended core outcome domains: (1) More recently published trials; (2) Trials published by corresponding authors from North America; (3) Trials published in higher impact journals;[1] and (4) Trials that began recruiting participants ≥1 year after publication of IMMPACT outcome recommendations. We estimated the date that patient recruitment began for trials that did not report this information by calculating the median duration from the beginning

of the recruitment period to the date of publication among trials that did report this information, then subtracting this value from the date of publication among trials that required imputation.

We fit one model per IMMPACT domain that showed sufficient variability in reporting; specifically, we did not consider domains that were reported less than 10% of the time or greater than 90% of the time. We tested for multicollinearity to examine whether any predictors were correlated. Specifically, we calculated the variance inflation factors (VIFs) associated with each independent variable in each regression model, and considered values ≥5 to indicate the presence of multicollinearity. If we detected multicollinearity between 2 or more variables, we removed the variable(s) that we deemed of lower importance. For all analyses, we calculated odds ratios (ORs) and the associated 95% confidence intervals (CIs), and set the level of significance at $p \leq 0.05$.

Our secondary objective was to explore the extent to which the trials reporting IMMPACT core domains used patient-reported outcome measures, or otherwise, i.e. clinician-reported, proxy-reported, or a combination.

We conducted all statistical analyses using IBM SPSS Statistics software (version 20).

RESULTS

Study characteristics

Our searches yielded 23,156 unique citations, of which we deemed 156 English-language studies eligible. No two articles resulted from the same trial. The chance-independent agreement was 0.77, representing substantial agreement. Table 1 summarizes the characteristics of these trials, and eTable 1 provides details regarding the clinical population under study, the intervention, and most commonly reported adverse events. Typical studies originated from the United States (42.3%), reported a funding source (57.1%), which was usually an industry sponsor (66.3%), and did not report registering their protocol (91.0%). Of the 14 trials with a registered protocol, authors of 12 trials (85.7%) reported at least one more outcome domain in the eventual publication than was reported in their protocol, and 1 (7%) failed to report an outcome specified in their protocol (eTable 2).The median impact factor of the journals (n=147) in which the trials were published was 2.8 (IQR: 2.2 to 5.6). The median sample size used for the primary analyses in the trials was 61 participants (IQR: 31 to 210). Of the trials published after 2004, 95.2% did not refer to the 2003 IMMPACT consensus statement. The median duration from start of participant recruitment to publication, among the 43 trials that reported this information, was 1402 days (IQR: 1005 to 2160).

Overall reporting

Trials most commonly reported pain (98.7%), and symptoms and adverse events (93.6%), whereas they least reported interpersonal functioning (7.1%) (Table 2). With the exception of pain, symptoms and adverse events, and participant disposition, fewer than half of all trials reported any of the other 6 IMMPACT-recommended core outcome domains.

Source of outcome information

Pain (79.9%) and physical functioning (59.2%) were most frequently reported by patients only (Table 3). In over half of eligible trials, both patients and clinicians provided information on participants' impressions of improvement and satisfaction with treatment. The source of outcome information was often unclear.

Factors associated with adherence to individual core outcome domains

After fitting the data using multiple linear regression models, we found that the associated VIFs for all the independent variables were less than 2. Pain relief, and symptoms and adverse events, were reported in over 90% of trials, and interpersonal functioning in fewer than 10%; as such, we did not fit models with these three domains.

Recently published trials were more likely to report the following outcome domains than older trials: physical functioning (OR: 2.3; 95% CI: 1.1, 4.8; p=0.03); emotional functioning (OR: 2.9; 95% CI: 1.5, 5.7; p<0.01); role functioning (OR: 2.5; 95% CI: 1.3, 4.8; p<0.01); sleep and fatigue (OR: 3.1, 95% CI: 1.8, 5.4; p<0.01); and, participant disposition (OR: 2.4, 95% CI: 1.5, 3.7; p<0.01).

Trials published by corresponding authors from North America were more likely to report the following outcome domains than trials originating elsewhere: physical functioning (OR: 2.5; 95% CI: 1.2, 4.8; p<0.01), participant ratings of improvement and satisfaction with treatment (OR: 2.4; 95% CI: 1.2, 5.0; p=0.02).

Compared to trials published in journals with lower impact factors, trials published in journals with higher impact factors were more likely to report treatment effects on emotional function (OR: 1.3; 95% CI: 1.1, 1.6; p<0.01), but less likely to report participant ratings of improvement and satisfaction with treatment (OR: 0.8; 95% CI: 0.7, 0.9; p<0.01).

Among trials that began recruiting participants after December 2004, i.e. one year after publication of the original six IMMPACT recommendations, we did not find any statistically significant associations between publication of the

IMMPACT recommendations and outcome reporting (Appendix). As no eligible trials began recruiting participants after July 2009, i.e. one year after publication of the later three IMMPACT recommendations, we could not explore for associations between publication of the IMMPACT recommendations and outcome reporting.

DISCUSSION

Findings

Almost all trials evaluating the use of opioids for chronic non-cancer pain reported effects on pain, and symptoms and adverse events. However, fewer than half of eligible trials evaluated treatment effects across six of the nine IMMPACT-recommend core outcome domains: physical functioning, participant ratings of improvement and satisfaction with treatment, sleep and fatigue, emotional functioning, role functioning, and interpersonal functioning. With the exception of participant ratings of global improvement, and pain, and adverse events, which we could not explore due to insufficient variability, our adjusted analyses found that all IMMPACT domains showed an increased rate of reporting over time. Publication of the IMMPACT recommendations was not associated with more complete reporting of IMMPACT core domains.

Strengths and Limitation

The strengths of our study include systematic searches of several electronic databases. Teams of reviewers conducted all subjective processes, including determining trial eligibility, and data collection, independently and in duplicate. To guard against spurious associations, we specified independent variables for regression models *a priori*, including the anticipated direction of association.

As we only looked at trials of opioids for CNCP, a limitation of our study is that our findings may not be generalizable to other chronic pain clinical trials.

Implications

Our study is the first to systematically evaluate adherence to IMMPACT-recommended outcome domains. We found that, although most IMMPACT domains showed an increased rate of reporting over time, most domains remained unreported by over half of all trials evaluating the effects of opioids for chronic non-cancer pain. Publication of the IMMPACT recommendations was not associated with increased reporting of IMMPACT-recommended core outcome domains, which is contrary to the belief held by some observers[16].

Without consistent and more complete reporting of patient-important outcomes in RCTs for chronic pain, trialists will be unable to fully convey the effects of a given treatment. Some may argue that reporting effects on pain relief and symptoms and adverse events provides sufficient information about a treatment's merits and risks. While there is empirical evidence that suggests a relationship between pain and other patient-important outcomes [14; 15; 21], differences in the magnitude and direction of treatment effects between outcome domains remain plausible. For instance, a previous systematic review of clinical trials of opioids for CNCP showed that, when compared to placebo,

the effects of opioids on pain relief is more than twice as great as their effects on functional gains.[6] Further, in evaluating the effectiveness of treatments for their pain, patients have identified aspects of their daily lives that go beyond pain and symptoms and adverse events.[18]

However, the reporting of large numbers of subjective outcomes is not without its problems. Comprehensive measurement of nine different domains may threaten the feasibility of a trial. Patients, for instance, may experience the requirement to complete these measures as an onerous burden; this may lead to a considerable amount of missing data, including for outcomes that are most important to patients. Further, trialists may think it unlikely for a treatment to have important effects on multiple outcome domains, especially within studies that follow patients for short time periods, i.e. less than 2 weeks. In addition, trialists (and systematic reviewers) may find sifting through large amounts of outcome information and synthesizing treatment effects in a succinct and easily digestible manner an overwhelming task. In recognition of this issue, the Grading of Recommendations Assessment, Development and Evaluation Working Group has recommended that systematic reviewers present no more than 7 outcomes in Summary of Findings tables.[9] Such considerations, and a corresponding desire to focus on the outcomes that patients consider most important, may underlie investigators' decisions not to measure all IMMPACT-recommended domains.

Exploration of reasons why chronic pain clinical trialists do not include comprehensive measurement of all domains, and improved guidance from IMMPACT to address potential feasibility concerns, warrant attention.

FOOTNOTES

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Table 1. Study characteristics

Country of Study (n=156), n (%)	
United States	66 (42.3%)
United Kingdom	18 (11.5%)
Canada	16 (10.3%)
France	8 (5.1%)
Germany	8 (5.1%)
Sweden	8 (5.1%)
Australia	5 (3.2%)
Italy	4 (2.5%)
Belgium	3 (1.9%)
Norway	3 (1.9%)
Denmark	2 (1.3%)
Other[1]	15 (9.5%)
Impact factor (n=147),[2] median (IQR)	2.8 (2.2 to 5.6)
Funding (n=156), n (%)	
Not reported	67 (42.9%)
Exclusively industry-funded	59 (37.8%)
Partially industry-funded	7 (4.5%)
Funded by non-Industry	22 (14.1%)
Not funded	1 (0.6%)
Protocol Registration (n=156), n (%)	
Not registered	142 (91.0%)
Registered	14 (9.0%)
Sample size for analysis (n=156), median (IQR)	61 (31 to 210)
Reference to IMMPACT recommendations among RCTs published from 2004 onwards (n=63), n (%)	3 (4.8%)

[1]2 studies each from Korea, Switzerland, and Turkey; 1 study each from Austria, Brazil, China, Czech Republic, Netherlands, Pakistan, Scotland, South Africa, and Venezuela

[2]7 journals, representing 9 publications, did not have impact factors recorded in the Web of Science's Science Citation Index

IQR = interquartile range
RCT = randomized controlled trial

Table 2. Reporting of IMMPACT-recommended core outcome domains

Outcome Domain	Number of trials (n=156)
Pain	154 (98.7%)
Symptoms and adverse events	146 (93.6%)
Participant disposition	118 (75.6%)
Physical functioning	71 (45.5%)
Participant ratings of improvement and satisfaction with treatment	67 (42.9%)
Sleep and fatigue	49 (31.0%)
Emotional functioning	44 (28.2%)
Role functioning	29 (18.6%)
Interpersonal functioning	11 (7.1%)

Table 3. Source of information for IMMPACT-recommended core outcome domains

Outcome Domain (number of trials)	Patient-reported	Clinician-reported	Patient- and clinician-reported	Not clear
Pain (n=154)	123 (79.9%)	1 (0.6%)	6 (3.9%)	24 (15.6%)
Physical functioning (n=71)	42 (59.2%)	2 (2.8%)	1 (1.4%)	26 (36.6%)
Emotional functioning (n=44)	21 (47.7%)	0	0	23 (52.3%)
Participant ratings of improvement and satisfaction with treatment (n=67)	24 (35.8%)	8 (11.9%)	33 (49.3%)	2 (3.0%)
Symptoms and adverse events (n=146)	61 (41.8%)	8 (5.5%)	74 (50.7%)	3 (2.1%)
Role functioning (n=29)	13 (44.8%)	0	1 (3.4%)	15 (51.7%)
Interpersonal functioning (n=11)	5 (45.5%)	0	1 (9.1%)	5 (45.5%)
Sleep and fatigue (n=49)	39 (79.6%)	0	0	10 (20.4%)

eTable 1. Detailed characteristics of eligible trials

Study	Clinical condition(s)	Generic name of opioid	Dosage of opioid treatment	Frequency of opioid treatment	Duration of opioid treatment	Route of administration of opioid treatment	Top 3* most commonly reported adverse events *when available
Afilalo M, Etropolski MS, Kuperwasser B, Kelly K, Okamoto A, Van Hove I, Steup A, Lange B, Rauschkolb C, Haeussler J. Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee. Clin Drug Investig 2010;30(8):489-505.	Chronic pain due to osteoarthritis (knee)	Tapentadol (extended-release) or oxycodone (controlled-release)	Tapentadol (extended-release): 100 to 250 mg; oxycodone (controlled-release): 20 to 50 mg	2 times daily	15 weeks	Oral	Constipation, nausea, dizziness
Arkinstall W, Sandler A, Goughnour B, Babul N, Harsanyi Z, Darke AC. Efficacy of controlled-release codeine in chronic non-malignant pain: a randomized, placebo-controlled clinical trial. Pain 1995;62(2):169-178.	Various chronic non-cancer pain conditions	Codeine (controlled-release)	100, 150 or 200 mg	2 times daily	7 days	Oral	Nausea, headache, constipation/dizziness
Arner S, Meyerson BA. Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. Pain 1988;33(1):11-23.	Various chronic non-cancer pain conditions	Morphine	15 mg for patients with neuropathic pain; 10-20 mg for idiopathic pain	1 time treatment	1 time treatment	Intravenous	Not reported
Attal N, Guirimand F, Brasseur L, Gaude V, Chauvin M, Bouhassira D. Effects of IV morphine in central pain: a randomized placebo-controlled study. Neurology 2002;58(4):554-563.	Central neuropathic pain (due to stroke or spinal cord injury)	Morphine	Initial dose was set according to maximum tolerable dose during run-in period	1 time treatment	1 time treatment	Intravenous	Somnolence, vomiting, nausea
Babul N, Noveck R, Chipman H, Roth SH, Gana T, Albert K. Efficacy and safety of extended-release, once-daily tramadol in chronic pain: a randomized 12-week clinical trial in osteoarthritis of the knee. J Pain Symptom Manage 2004;28(1):59-71.	Chronic pain due to osteoarthritis (knee)	Tramadol (extended-release)	100 mg (initial dose) increased to 200 mg between days 4 and 8 of treatment, and further increased to 300 mg or 400 mg after first week (depending on tolerability)	1 time daily	12 weeks	Oral	Dizziness, nausea, constipation

Beaulieu AD, Peloso PM, Haraoui B, Bensen W, Thomson G, Wade J, Quigley P, Eisenhoffer J, Harsanyi Z, Darke AC. Once-daily, controlled-release tramadol and sustained-release diclofenac relieve chronic pain due to osteoarthritis: a randomized controlled trial. Pain Res Manag 2008;13(2):103-110.	Chronic pain due to osteoarthritis	Tramadol (controlled-release)	200 mg (initial dose) titrated weekly to 200, 300, 400 mg (maximum dose)	1 time daily	6 weeks	Oral	Dizziness, nausea, constipation
Bennett RM, Kamin M, Karim R, Rosenthal N. Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. Am J Med 2003;114(7):537-545.	Fibromyalgia	Combination of tramadol / acetaminophen	37.5 mg	1 to 2 tablets (4 time daily) for a maximum of 8 tablets	91 days	Oral	Nausea, dizziness, somnolence
Biasi G, Manca S, Manganelli S, Marcolongo R. Tramadol in the fibromyalgia syndrome: a controlled clinical trial versus placebo. Int J Clin Pharmacol Res 1998;18(1):13-19.	Fibromyalgia	Tramadol	100 mg per 2 mL	1 time treatment	1 time treatment	Intravenous	Nausea, somnolence, epigastric pain
Blondell RD, Ashrafioun L, Dambra CM, Foschio EM, Zielinski AL, Salcedo DM. A clinical trial comparing tapering doses of buprenorphine with steady doses for chronic pain and co-existent opioid addiction. J Addict Med 2010;4(3):140.	Various chronic non-cancer pain conditions	Combination of buprenorphine / naloxone	2 mg	3-4 times daily, up to 16 mg daily	6 months	Oral	None reported
Bohme K. Buprenorphine in a transdermal therapeutic system--a new option. Clin Rheumatol 2002;21 Suppl 1:S13-16.	Various chronic non-cancer pain conditions	Buprenorphine	Study 1: 0.8-1.2 mg Study 2: 35, 52.5, or 70 µg (per hour) Study 3: 35 µg (per hour)	Study 1: 2 patch applications Study 2: 5 patch applications Study 3: 3 patch applications	Study 1: 6 days Study 2: 15 days Study 3: 9 days	Transdermal patch	Nausea, vomiting, dizziness
Borges J, Zavaleta C. Study of a new analgesic compound in the treatment of tension headache. J Int Med Res 1976;4(1):74-78.	Tension headache	Combination of hydroxyzine / acetaminophen / propoxyphene / caffeine	Propoxyphene: 30 mg	1-2 tablets (initial dose) increased to 1 tablet every 4-6 hours daily	4 weeks	Oral	Drowsiness, dizziness

Boureau F, Boccard E. Placebo-controlled study of the analgesic efficacy of a combination of paracetamol and codeine in rheumatoid arthritis. Acta Ther 1991;17(2):123-136.	Chronic pain due to rheumatoid arthritis	Combination of paracetamol / codeine	Codeine: 30 mg	1 tablet, 3 times daily	7 days	Oral	Constipation, nausea, vomiting
Boureau F, Delecoeuillerie G, Orvain J. Comparative study of the efficacy and tolerance of 2 dosages of the paracetamol 400 mg codeine 25 mg association versus paracetamol 1000 mg in non-inflammatory rheumatic pain. Revue internationale de rhumatologie 1990;20(96):41-47.	Chronic non-inflammatory rheumatic pain	Combination of paracetamol / codeine	Codeine: 25 mg or 50 mg	Every 6 hours if necessary for pain relief up to 100 mg/day	3 days	Oral	Nausea, constipation, drowsiness
Boureau F, Legallicier P, Kabir-Ahmadi M. Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial. Pain 2003;104(1-2):323-331.	Postherpetic neuralgia	Tramadol (sustained-release)	100 mg	1 time daily up to 4 times daily	6 weeks	Oral	Nausea, constipation
Breivik H, Ljosaa TM, Stengaard-Pedersen K, Persson J, Aro H, Villumsen J, Tvinnemose D. A 6-months, randomised, placebo-controlled evaluation of efficacy and tolerability of a low-dose 7-day buprenorphine transdermal patch in osteoarthritis patients naïve to potent opioids. Scandinavian Journal of Pain 2010;1(3):122-141.	Chronic pain due to osteoarthritis	Buprenorphine	5 µg per hour (initial dose) titrated to 10 or 20 µg per hour, as needed	1 patch lasting 7 days	6 months	Transdermal patch	Nausea, vomiting, constipation
Burch F, Fishman R, Messina N, Corser B, Radulescu F, Sarbu A, Craciun-Nicodin MM, Chiriac R, Beaulieu A, Rodrigues J. A comparison of the analgesic efficacy of Tramadol Contramid OAD versus placebo in patients with pain due to osteoarthritis. J Pain Symptom Manage 2007;34(3):328-338.	Chronic pain due to osteoarthritis (knee)	Tramadol	100 mg (initial dose) titrated in 100 mg increments up to 300 mg	Not reported	12 weeks	Oral	Nausea, constipation, dizziness/vertigo

Buynak R, Shapiro DY, Okamoto A, Hove IV, Rauschkolb C, Steup A, Lange B, Lange C, Etropolski M. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo-and active-controlled Phase III study. Expert Opin Pharmacother 2010;11(11):1787-1804.	Chronic low back pain	Tapentadol (extended-release) or oxycodone (controlled-release)	Tapentadol (extended-release): 100 to 250 mg; oxycodone (controlled-release): 20 to 50 mg	2 times daily	15 weeks	Oral	Nausea, constipation, headache
Caldwell JR, Hale ME, Boyd RE, Hague JM, Iwan T, Shi M, Lacouture PG. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. J Rheumatol 1999;26(4):862-869.	Chronic pain due to osteoarthritis	Oxycodone (controlled-release) or combination of oxycodone (immediate-release) / acetaminophen	Oxycodone (controlled-release): 10 mg; combination treatment: 5-325 mg	Oxycodone (controlled-release): 2 times daily; combination treatment: 4 times daily	60 days	Oral	Nausea, vomiting, drowsiness
Caldwell JR, Rapoport RJ, Davis JC, Offenberg HL, Marker HW, Roth SH, Yuan W, Eliot L, Babul N, Lynch PM. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. J Pain Symptom Manage 2002;23(4):278-291.	Chronic pain due to osteoarthritis (knee or hip)	Morphine (extended-release)	30 mg	1 time daily	4 weeks	Oral	Constipation, nausea, diarrhea
Castagnera L, Maurette P, Pointillart V, Vital JM, Erny P, Senegas J. Long-term results of cervical epidural steroid injection with and without morphine in chronic cervical radicular pain. Pain 1994;58(2):239-243.	Chronic cervical radicular pain	Combination of morphine and steroid	Morphine: 2.5 mg	1 time treatment	1 time treatment	Intravenous	Pruritus, nausea, dizziness

Corsinovi L, Martinelli E, Fonte G, Astengo M, Sona A, Gatti A, Massaia M, Bo M, Zanocchi M, Michelis G, Isaia G, Molaschi M. Efficacy of oxycodone/acetaminophen and codeine/acetaminophen vs. conventional therapy in elderly women with persistent, moderate to severe osteoarthritis-related pain. Arch Gerontol Geriatr 2009;49(3):378-382.	Chronic pain due to osteoarthritis	Combination of oxycodone (immediate-release) / acetaminophen or combination of codeine (controlled-release) / acetaminophen	Oxycodone (in combination treatment): 5mg; codeine (in combination treatment): 30mg	Oxycodone: 2 times daily; codeine: 3 times daily	6 weeks	Oral	Nausea, vomiting, drowsiness
Dallas T, Lin R, Wu W, Wolskee P. Epidural morphine and methylprednisolone for low-back pain. Anesthesiology 1987;67(3):408.	Chronic low back pain	Morphine	8 mg per 8 mL of saline	1 time treatment	1 time treatment	Injection (epidural)	Pruritus, mild nausea/vomiting, urinary retention
Dapoigny M, Abitbol JL, Fraitag B. Efficacy of peripheral kappa agonist fedotozine versus placebo in treatment of irritable bowel syndrome. A multicenter dose-response study. Dig Dis Sci 1995;40(10):2244-2249.	Irritable Bowel Syndrome	Fedotozine	3.5, 15, or 30 mg	3 times daily	6 weeks	Oral	Headache, vertigo, fatigue
de Craen AJ, Lampe-Schoenmaeckers AJ, Kraal JW, Tijssen JG, Kleijnen J. Impact of experimentally-induced expectancy on the analgesic efficacy of tramadol in chronic pain patients: a 2 x 2 factorial, randomized, placebo-controlled, double-blind trial. J Pain Symptom Manage 2001;21(3):210-217.	Various chronic non-cancer pain conditions	Tramadol	50 mg	1 time treatment	1 time treatment	Oral	Nausea, vomiting, dizziness
Doak W, Hosie J, Hossain M, James I, Reid I, Miller A. A novel combination of ibuprofen and codeine phosphate in the treatment of osteoarthritis: A double-blind placebo controlled study. J Drug Dev 1992;4:179-187.	Chronic pain due to osteoarthritis (hip or knee)	Combination of ibuprofen (controlled-release) / codeine (normal release)	Codeine: 20 mg	2 tablets, 2 times daily	1 week	Oral	Constipation, severe dizziness

Eide PK, Jorum E, Stubhaug A, Bremnes J, Breivik H. Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. Pain 1994;58(3):347-354.	Postherpetic neuralgia	Morphine	0.075 mg/kg	1 time treatment	1 time treatment	Intravenous	Fatigue, dizziness, feeling of unreality
Eisenach JC, Carpenter R, Curry R. Analgesia from a peripherally active κ-opioid receptor agonist in patients with chronic pancreatitis. Pain 2003;101(1):89-95.	Chronic pain due to pancreatitis	ADL 10-0101 (κ-opioid receptor agonist)	10 µg	2 infusions sessions	60 minutes	Intravenous	No side effects reported
Emkey R, Rosenthal N, Wu SC, Jordan D, Kamin M. Efficacy and safety of tramadol/acetaminophen tablets (Ultracet) as add-on therapy for osteoarthritis pain in subjects receiving a COX-2 nonsteroidal antiinflammatory drug: a multicenter, randomized, double-blind, placebo-controlled trial. J Rheumatol 2004;31(1):150-156.	Chronic pain due to osteoarthritis (knee or hip)	Combination of tramadol / acetaminophen	37.5 mg	1 table (every 3 days) to a maximum of 8 tablets daily	91 days	Oral	Nausea, constipation, dizziness
Etropolski M, Kelly K, Okamoto A, Rauschkolb C. Comparable efficacy and superior gastrointestinal tolerability (nausea, vomiting, constipation) of tapentadol compared with oxycodone hydrochloride. Adv Ther 2011;28(5):401-417.	Various chronic pain conditions	Tapentadol (immediate-release) or oxycodone (immediate-release)	Tapentadol (immediate-release): 50 mg or 75 mg; oxycodone (immediate-release): 10 mg	1 tablet, 4-6 times daily	28 days	Oral	Nausea, constipation, vomiting
Fancourt GJ, Flavell Matts SG. A double-blind comparison of meptazinol versus placebo in chronic rheumatoid arthritis and osteoarthritis. Curr Med Res Opin 1984;9(3):184-191.	Chronic pain due to rheumatoid arthritis and osteoarthritis	Meptazinol	200 mg	1 tablet every 3-6 hours	72 hours	Oral	Nausea, giddy/dizzy/lightheaded, vomiting
Farrar JT, Messina J, Xie F, Portenoy RK. A Novel 12-Week Study, with Three Randomized, Double-Blind Placebo-Controlled Periods to Evaluate Fentanyl Buccal Tablets for the Relief of Breakthrough Pain in	Various chronic non-cancer pain conditions	Fentanyl	Initial dose was set according to the dose that provided stable pain control during the run-in phase	Up to 8 times daily	12 weeks	Oral	Nausea, dizziness, somnolence

Opioid-Tolerant Patients with Noncancer-Related Chronic Pain. Pain Med 2010;11(9):1313-1327.							
Fleischmann RM, Caldwell JR, Roth SH, Tesser JR, Olson W, Kamin M. Tramadol for the treatment of joint pain associated with osteoarthritis: a randomized, double-blind, placebo-controlled trial. Current Therapeutic Research 2001;62(2):113-128.	Chronic pain due to osteoarthritis (knee)	Tramadol	50 mg (initial dose) titrated in 50 mg increments to a target dose of 200 mg daily	1 tablet, 4 times daily	91 days	Oral	Nausea, constipation, dizziness
Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. BMJ 2008;336(7637):199-201.	Chronic neuropathic pain	Dihydrocodeine	30 mg (initial dose) titrated weekly to 60, 120, 240 mg (maximum dose)	1 time daily	6 weeks	Oral	Tiredness, sleeplessness, sickness
Freeman R, Raskin P, Hewitt DJ, Vorsanger GJ, Jordan DM, Xiang J, Rosenthal NR. Randomized study of tramadol/acetaminophen versus placebo in painful diabetic peripheral neuropathy. Curr Med Res Opin 2007;23(1):147-161.	Painful diabetic neuropathy	Combination of tramadol / acetaminophen	Tramadol: 37.5 mg (initial dose) (suggested titration schedule: one tablet at bedtime as needed on Days 1–3; one tablet twice daily as needed on Days 4–6; one tablet three times daily as needed on Days 7–9; and one tablet four times daily as needed on Day 10)	Up to 1–2 tablets 4 times daily	66 days	Oral	Nausea
Friedman A, Boyles W, Elkind A, Fillingim J, Ford R, Gallagher R, Hobbs D, Rapoport A, Richards B, Sheftell F. Fiorinal with codeine in the treatment of tension headache--the contribution of components to the combination drug. Clin Ther 1987;10(3):303-315.	Tension headache	Codeine-alone or combination of butalbital / caffeine / aspirin / codeine	Codeine: 30 mg (alone or combination treatment)	2 tablets	4 hours	Oral	Nausea, vomiting, gastrointestinal events

Friedman AP, DiSerio FJ. Symptomatic treatment of chronically recurring tension headache: a placebo-controlled, multicenter investigation of Fioricet and acetaminophen with codeine. Clin Ther 1987;10(1):69-81.	Tension headache	Combination of acetaminophen / codeine	Not reported	2 capsules at 5 designated times over a 4 hour period	4 hours	Oral	Dizziness, nausea, abdominal discomfort
Friedman AP. Assessment of Fiorinal with Codeine in the treatment of tension headache. Clin Ther 1986;8(6):703-721.	Tension headache	Codeine-alone or combination of butalbital / caffeine / aspirin / codeine	Codeine: 30 mg (alone or combination treatment)	4 capsules (2 per headache within 24 hrs of each other) daily	4 hours	Oral	Not reported
Friedmann N, Klutzaritz V, Webster L. Efficacy and safety of an extended-release oxycodone (Remoxy) formulation in patients with moderate to severe osteoarthritic pain. J Opioid Manag 2010;7(3):193-202.	Chronic pain due to osteoarthritis	Oxycodone (extended-release)	20 mg (initial dose) titrated down to prevent opioid withdrawal	1 tablet, 2 times daily	12 weeks	Oral	Nausea, constipation, somnolence
Gana TJ, Pascual ML, Fleming RR, Schein JR, Janagap CC, Xiang J, Vorsanger GJ. Extended-release tramadol in the treatment of osteoarthritis: a multicenter, randomized, double-blind, placebo-controlled clinical trial. Curr Med Res Opin 2006;22(7):1391-1401.	Chronic pain due to osteoarthritis (knee or hip)	Tramadol (extended-release)	100, 200, 300, or 400 mg; participants taking tramadol began with a dose of 100mg and the dose was to be titrated as follows: to 200mg on Day 5 (in the 200, 300, and 400mg groups), to 300mg on Day 10 (in the 300 and 400mg groups), and to 400mg on Day 15 (in the 400mg group).	1 time daily	12 weeks	Oral	Constipation, dizziness, nausea
Gawel MJ, Szalai JF, Stiglick A, Aimola N, Weiner M. Evaluation of analgesic agents in recurring headache compared with other clinical pain models. Clin Pharmacol Ther 1990;47(4):504-508.	Recurring headache	Codeine	8 mg	Single dose of 2 capsules	6 hours	Oral	None reported
Gazi MB, Sakata RK, Issy AM. Intra-articular morphine versus bupivacaine for knee motion among patients with osteoarthritis:	Chronic pain due to osteoarthritis (knee)	Morphine	1 mg	1 time treatment	1 time treatment	Intra-articular injection	Not reported

randomized double-blind clinical trial. Sao Paulo Med J 2008;126(6):309-313.							
Gerschman JA, Reade PD, Burrows GD. Evaluation of a proprietary analgesic/antihistamine in the management of pain associated with temporomandibular joint pain dysfunction syndrome. Aust Dent J 1984;29(5):300-304.	Temporomandibular join pain dysfunction syndrome	Combination of acetaminophen / codeine	Codeine: 9.75 mg	2 tablets every 4 hours	3 weeks	Oral	Drowsiness
Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med 2005;352(13):1324-1334.	Painful diabetic neuropathy or postherpetic neuralgia	Morphine (sustained-release) or combination of morphine (sustained-release) / gabapentin	Morphine (sustained-release): 30 mg; the target daily-dose ceilings were morphine at a dose of 120 mg (morphine-alone treatment), morphine at a dose of 60 mg (combination treatment)	2 times daily	5 weeks	Oral	Constipation, sedation, dry mouth
Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. Neurology 2003;60(6):927-934.	Painful diabetic neuropathy	Oxycodone (controlled-release)	10 mg daily (initial dose) daily to 60 mg (daily)	1 table (2 times daily) to 6 tablets (2 times daily)	6 weeks	Oral	Constipation, nausea, somnolence
Glowinski J, Boccard E. Placebo-Controlled Study of the Analgesic Efficacy of a Paracetamol 500mg/Codeine 30mg Combination Together with Low-Dose vs High-Dose Diclofenac in Rheumatoid Arthritis. Clin Drug Investig 1999;18(3):189-197.	Chronic pain due to rheumatoid arthritis	Combination of paracetamol / codeine	Codeine: 30 mg	1 tablet, 3 times daily	7 days	Oral	Abdominal pain, malaise, pruritus
Glynn C, Dawson D, Sanders R. A double-blind comparison between epidural morphine and epidural clonidine in patients with chronic non-cancer pain. Pain 1988;34(2):123-128.	Various chronic non-cancer pain conditions	Morphine	5 mg	1 time treatment	1 time treatment	Injection (epidural)	Pruritus, nausea, vomiting

Göbel H, Stadler T. Treatment of pain due to postherpetic neuralgia with tramadol. Clin Drug Investig 1995;10(4):208-214.	Postherpetic neuralgia	Tramadol	50 mg	1 tablet 4 times daily (up to 2-3 tablets, if insufficient analgesia)	6 weeks	Oral	Nausea, vomiting, dizziness
Gordon A, Callaghan D, Spink D, Cloutier C, Dzongowski P, O'Mahony W, Sinclair D, Rashiq S, Buckley N, Cohen G. Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. Clin Ther 2010;32(5):844-860.	Chronic low back pain	Buprenorphine	5 µg per hour (initial dose) titrated weekly to 10 µg per hour and 20 µg per hour	1 patch lasting 7 days	4 weeks	Transdermal patch	Nausea, somnolence, pruritus
Gordon A, Rashiq S, Moulin DE, Clark AJ, Beaulieu AD, Eisenhoffer J, Piraino PS, Quigley P, Harsanyi Z, Darke AC. Buprenorphine transdermal system for opioid therapy in patients with chronic low back pain. Pain Research & Management: The Journal of the Canadian Pain Society 2010;15(3):169.	Chronic low back pain	Buprenorphine	10 µg per hour (initial dose) titrated weekly to 20 µg per hour and maximum of 40 µg per hour	Patches changed every 6 to 8 days	4 weeks	Transdermal patch	Nausea, dizziness, pruritus
Gross DP, Bhambhani Y, Haykowsky MJ, Rashiq S. Acute opioid administration improves work-related exercise performance in patients with chronic back pain. J Pain 2008;9(9):856-862.	Chronic back pain	Fentanyl	1 µg/kg	1 time treatment	1 time treatment	Intravenous	Nausea
Group GPR. Migraine treated with an antihistamine-analgesic combination. Practitioner 1973;211(263):357-361.	Migraine	Combination of buclizine / paracetamol / codeine or combination of paracetamol / codeine	Codeine: 8 mg (both combinations)	2 tablets per attack (initial dose), 0.5 tablet at 30 minute intervals, up to a maximum of 4 tablets per attack	24 hours	Oral	Nausea, dizziness
Hakkarainen H, Quiding H, Stockman O. Mild analgesics as an alternative to ergotamine in migraine. A comparative trial with acetylsalicylic acid, ergotamine tartrate, and a dextropropoxyphene compound. J Clin	Migraine	Combination of dextropropoxyphene / acetylsalicylic acid / antipyrine	Dextropropoxyphene: 100 mg	7 times	Variable (treatment given for 7 migraine attacks)	Oral	Nausea, vomiting, dizziness

Pharmacol 1980;20(10):590-595.							
Hale M, Khan A, Kutch M, Li S. Once-daily OROS hydromorphone ER compared with placebo in opioid-tolerant patients with chronic low back pain. Curr Med Res Opin 2010;26(6):1505-1518.	Chronic low back pain	Hydromorphone (extended-release)	Initial dose was set according to the dose that provided stable pain control during the run-in phase	1 time daily	12 weeks	Oral	Nausea, constipation, drug withdrawal symptoms
Hale ME, Ahdieh H, Ma T, Rauck R. Efficacy and safety of OPANA ER (oxymorphone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: a 12-week, randomized, double-blind, placebo-controlled study. J Pain 2007;8(2):175-184.	Chronic low back pain	Oxymorphone (extended-release)	Initial dose was 2 times daily dose of opioid that was approximately equivalent to the dosage of opioid that patients were receiving at screening. If the starting dose did not provide adequate pain relief, patients were to be titrated up by 10-mg (twice daily) increments every 3 to 7 days until a stabilized dose was reached.	2 times daily	12 weeks	Oral	Constipation, somnolence, nausea
Hale ME, Dvergsten C, Gimbel J. Efficacy and safety of oxymorphone extended release in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study. J Pain 2005;6(1):21-28.	Chronic low back pain	Oxymorphone (extended-release) or oxycodone (controlled-release)	Oxymorphone (extended-release): 10 mg (initial dose) titrated to 110 mg; oxycodone (controlled-release): 20 mg (initial dose) titrated to 220 mg	2 times daily	7 to 14 days	Oral	Constipation, sedation
Hanna M, O'Brien C, Wilson MC. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. Eur J Pain 2008;12(6):804-813.	Painful diabetic neuropathy	Oxycodone (prolonged-release)	5 mg	2 times daily	12 weeks	Oral	Constipation, nausea, fatigue

Harati Y, Gooch C, Swenson M, Edelman S, Greene D, Raskin P, Donofrio P, Cornblath D, Sachdeo R, Siu CO, Kamin M. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology 1998;50(6):1842-1846.	Painful diabetic neuropathy	Tramadol	100 mg daily (initial dose) increased over 28 days to a maximum of 400 mg daily	4 times daily	42 days	Oral	Nausea, constipation, headache
Harke H, Gretenkort P, Ladleif HU, Rahman S, Harke O. The response of neuropathic pain and pain in complex regional pain syndrome I to carbamazepine and sustained-release morphine in patients pretreated with spinal cord stimulation: a double-blinded randomized study. Anesth Analg 2001;92(2):488-495.	Chronic neuropathic pain	Morphine (sustained-release)	30 mg	3 times daily	At least 8 days	Oral	Constipation, fatigue, sweating
Hartrick C, Van Hove I, Stegmann J-U, Oh C, Upmalis D. Efficacy and tolerability of tapentadol immediate release and oxycodone HCl immediate release in patients awaiting primary joint replacement surgery for end-stage joint disease: a 10-day, phase III, randomized, double-blind, active-and placebo-controlled study. Clin Ther 2009;31(2):260-271.	Chronic pain due to joint disease	Tapentadol (immediate-release), or oxycodone (immediate-release)	Tapentadol (immediate-release): 50 mg or 75 mg; oxycodone (immediate-release): 10 mg	1 tablet, 4-6 hours daily	10 days	Oral	Dizziness, nausea, vomiting
Hill RC, Turner P. A comparison of codeine compound and "saridone" in the pain of rheumatoid arthritis. Br J Clin Pract 1970;24(1):29-32.	Chronic pain due to rheumatoid arthritis	Combination of acetylsalicylic acid / phenacetin / codeine	Codeine: 8 mg	2 tablets daily	4 days	Oral	Vertigo, drowsiness
Ho T, Backonja M, Ma J, Leibensperger H, Froman S, Polydefkis M. Efficient assessment of neuropathic pain drugs in patients with small fiber sensory neuropathies. PAIN® 2009;141(1):19-24.	Chronic neuropathic pain	Tramadol	50 mg	4 times daily	2 weeks	Oral	Dizziness, nausea, dyspepsia

Huse E, Larbig W, Flor H, Birbaumer N. The effect of opioids on phantom limb pain and cortical reorganization. Pain 2001;90(1-2):47-55.	Phantom limb pain	Morphine	Not reported	Not reported	8 weeks	Oral	Tiredness, dizziness, sweating
Huskisson E. Simple analgesics for arthritis. BMJ 1974;4(5938):196-200.	Chronic pain due to rheumatoid arthritis	Trial I: Combination of paracetamol / dextropropoxyphene Trial II: Combination of aspirin / codeine Trial III: Ciba 44,328 (new compound)	Trial I: Dextropropoxyphene: 32.5 mg) Trial II: Codeine: 8 mg Trial III: not reported	2 tablets daily	Trial I: 17 days Trial II: 17 days Trial III: 9 days	Oral	Not reported
Hwang DS, Mietlowski MJ, Friedman AP. Fiorinal with Codeine in the management of tension headache: impact of placebo response. Clin Ther 1987;9(2):201-222.	Tension headache	Codeine-alone or combination of butalbital / caffeine / aspirin / codeine	Codeine: 30 mg (alone or combination treatment)	4 capsules (2 per headache within 24 hrs of each other) daily	4 hours	Oral	Not reported
Ingpen ML. A controlled clinical trial of sustained-action dextropropoxyphene hydrochloride. Br J Clin Pract 1969;23(3):113-115.	Chronic pain due to degenerative joint disease of the spine & rheumatoid arthritis	Dextroproproxyphene (sustained-release)	150 mg	1 capsule every eight hours	4 days	Oral	Drowsiness, indigestion, dizziness
James I, Miller A. A combination of ibuprofen and codeine phosphate in the management of osteoarthritis: a double blind comparison with ibuprofen. BRITISH JOURNAL OF CLINICAL RESEARCH 1993;4:199-199.	Chronic pain due to osteoarthritis (hip or knee)	Combination of ibuprofen (controlled-release) / codeine (normal release)	Codeine: 20 mg	2 tablets, 2 times daily	1 week	Oral	Nausea, vomiting, abdominal pain
Jamison RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain. A randomized prospective study. Spine (Phila Pa 1976) 1998;23(23):2591-2600.	Chronic non-cancer back pain	Oxycodone or combination of oxycodone (titrated) / morphine (sustained-release)	Oxycodone-alone: 5 mg; combination treatment: oxycodone (dose not reported) and morphine (sustained-release) (maximum dose, 200 mg)	Oxycodone-alone: up to 4 doses daily; combination treatment: not reported	16 weeks	Oral	Dry mouth, drowsiness, headache
Jorum E, Warncke T, Stubhaug A. Cold allodynia and hyperalgesia in neuropathic pain: the effect of N-methyl-D-aspartate (NMDA) receptor antagonist ketamine--a double-blind, cross-over	Chronic neuropathic pain	Alfentanil	Bolus dose of 7 mg/kg and a continuous infusion at a rate of 0.6 mg/kg/min for 20 min	1 time treatment	1 time treatment	Intravenous	Nausea, fatigue, dizziness

comparison with alfentanil and placebo. Pain 2003;101(3):229-235.							
Kagan G, Masheter HC. A controlled study of short-term treatment of tension headache. Curr Med Res Opin 1978;5(9):709-713.	Tension headache	Combination of paracetamol / codeine / doxylamine succinate / caffeine	Codeine: 10 mg	2 tablets (initial dose) increased to 6 tablets every 4-6 hours daily	Variable (treatment given for 4 migraine attacks)	Oral	Drowsiness, nausea, insomnia
Katz N, Hale M, Morris D, Stauffer J. Morphine sulfate and naltrexone hydrochloride extended release capsules in patients with chronic osteoarthritis pain. Postgrad Med 2010;122(4):112-128.	Chronic pain due to osteoarthritis	Combination of morphine / naltrexone (extended-release)	20 mg daily, titrated to a maximum of 160 mg daily	1 to 2 times daily	12 weeks	Oral	Constipation, nausea, somnolence
Katz N, Rauck R, Ahdieh H, Ma T, Gerritsen van der Hoop R, Kerwin R, Podolsky G. A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naive patients with chronic low back pain. Curr Med Res Opin 2007;23(1):117-128.	Chronic low back pain	Oxymorphone (extended-release)	Patients received oxymorphone (extended-release) 5 mg every 12 h for 2 days; thereafter, patients were to be titrated at increments of 5–10 mg every 12 h every 3–7 days until dose stabilization was achieved	2 times daily	12 weeks	Oral	Constipation, nausea, somnolence
Kean WF, Bouchard S, Roderich Gossen E. Women with pain due to osteoarthritis: the efficacy and safety of a once-daily formulation of tramadol. Pain Med 2009;10(6):1001-1011.	Chronic pain due to osteoarthritis (knee)	Tramadol	100, 200, or 300 mg; all patients started with 100 mg daily; patients randomized to the 200 mg and 300 mg groups were titrated by 100 mg daily increments every 2-3 days until respective randomized dosages were achieved	1 time daily	12 weeks	Oral	Nausea, dizziness, constipation
Keskinbora K, Aydinli I. Perineural morphine in patients with chronic ischemic lower extremity pain: efficacy and long-term results. J	Chronic ischemic lower extremity pain	Combination of bupivacaine / morphine	Morphine: 10 mg in 20 mL saline	1 time treatment	1 time treatment	Intravenous	Somnolence, nausea

Anesth 2009;23(1):11-18.							
Khoromi S, Cui L, Nackers L, Max MB. Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. Pain 2007;130(1-2):66-75.	Chronic lumbar root pain	Morphine (sustained-release) or combination of morphine (sustained-release) / nortriptyline	Morphine (sustained-release): 15 mg (initial dose) 1 time daily to 2 times daily on 4th day, followed by 15 mg increase per week over next four weeks to 90 mg (maximum dose)	2 times daily	9 weeks	Oral	Constipation, dry mouth, drowsiness
Kivitz A, Ma C, Ahdieh H, Galer BS. A 2-week, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, phase III trial comparing the efficacy of oxymorphone extended release and placebo in adults with pain associated with osteoarthritis of the hip or knee. Clin Ther 2006;28(3):352-364.	Chronic pain due to osteoarthritis (knee or hip)	Oxymorphone (extended-release)	Oxymorphone 10 mg ; oxymorphone 20 mg (initial dose) titrated to 40 mg; oxymorphone 20 mg (initial dose) titrated to 50 mg	2 times daily	2 weeks	Oral	Nausea, vomiting, dizziness
Kjaersgaard-Andersen P, Nafei A, Skov O, Madsen F, Andersen HM, Kroner K, Hvass I, Gjoderum O, Pedersen L, Branebjerg PE. Codeine plus paracetamol versus paracetamol in longer-term treatment of chronic pain due to osteoarthritis of the hip. A randomised, double-blind, multi-centre study. Pain 1990;43(3):309-318.	Chronic pain due to osteoarthritis of the hip	Combination of codeine / paracetamol	Codeine: 60 mg	3 times daily	4 weeks	Oral	Nausea, dizziness, vomiting
Ko SH, Kwon HS, Yu JM, Baik SH, Park IB, Lee JH, Ko KS, Noh JH, Kim DS, Kim CH. Comparison of the efficacy and safety of tramadol/acetaminophen combination therapy and gabapentin in the treatment of painful diabetic neuropathy. Diabet Med 2010;27(9):1033-1040.	Painful diabetic neuropathy	Combination of tramadol / acetaminophen	Tramadol: 37.5mg	Combination treatment: 1 tablet/bedtime on Day 1, increased to 1 tablet/twice daily on Days 2-7, increased to 1 tablet/thrice daily on Days 8-14, maintained thereafter	6 weeks	Oral	Dizziness, drowsiness, nausea/vomiting

Kupers RC, Konings H, Adriaensen H, Gybels JM. Morphine differentially affects the sensory and affective pain ratings in neurogenic and idiopathic forms of pain. Pain 1991;47(1):5-12.	Various chronic non-cancer pain conditions	Morphine	Dose administered every 10 minutes to reach 0.3 mg/kg per day	1 time treatment	1 time treatment	Intravenous	Not reported
Laiq N, Khan MN, Iqbal MJ, Khan S. Comparison of epidural steroid injections with conservative management in patients with lumbar radiculopathy. J Coll Physicians Surg Pak 2009;19(9):539-543.	Lumbar radiculopathy	Tramadol	100 mg	1 time daily	6 months	Oral	None reported
Landau CJ, Carr WD, Razzetti AJ, Sessler NE, Munera C, Ripa SR. Buprenorphine transdermal delivery system in adults with persistent noncancer-related pain syndromes who require opioid therapy: a multicenter, 5-week run-in and randomized, double-blind maintenance-of-analgesia study. Clin Ther 2007;29(10):2179-2193.	Non-specific non-cancer-related pain	Buprenorphine	Initial dose was set according to the dose that provided stable pain control during the run-in phase	Not reported	5 weeks	Transdermal patch	Pruritus, headache, somnolence
Lane PL, McLellan BA, Baggoley CJ. Comparative efficacy of chlorpromazine and meperidine with dimenhydrinate in migraine headache. Ann Emerg Med 1989;18(4):360-365.	Migraine	Combination of meperidine / dimenhydrinate	Meperidine: 0.4 mg/kg	Every 15 min as needed up to 3 doses	45 minutes	Intravenous	Drowsiness, nausea/vomiting, dizziness
Langford R, McKenna F, Ratcliffe S, Vojtassak J, Richarz U. Transdermal fentanyl for improvement of pain and functioning in osteoarthritis: a randomized, placebo-controlled trial. Arthritis Rheum 2006;54(6):1829-1837.	Chronic pain due to osteoarthritis (knee or hip)	Fentanyl	25 µg/hour (initial dose) with increase, as required, at the rate of 1 extra patch every 3 days, up to a maximum of 4 patches	Patches were replaced every 72 hours	6 weeks	Transdermal patch	Nausea, application site reaction, headache
Larkin GL, Prescott JE. A randomized, double-blind, comparative study of the efficacy of ketorolac tromethamine versus meperidine in the treatment of severe migraine. Ann Emerg Med 1992;21(8):919-924.	Migraine	Meperidine	75 mg	1 time treatment	1 time treatment	Injection (intramuscular)	None reported

Lemming D, Sorensen J, Graven-Nielsen T, Lauber R, Arendt-Nielsen L, Gerdle B. Managing chronic whiplash associated pain with a combination of low-dose opioid (remifentanil) and NMDA-antagonist (ketamine). Eur J Pain 2007;11(7):719-732.	Chronic whiplash-associated pain	Remifentanil	1 and 2 ng/mL (stepwise) (target plasma concentration)	At least 1 time weekly	At least 4 weeks	Intravenous	Sedation, pruritus, nausea
Leung A, Wallace MS, Ridgeway B, Yaksh T. Concentration-effect relationship of intravenous alfentanil and ketamine on peripheral neurosensory thresholds, allodynia and hyperalgesia of neuropathic pain. Pain 2001;91(1-2):177-187.	Chronic neuropathic pain	Alfentanil	Target plasma levels of 25, 50 and 75 ng/ml	3 times, each one week apart	20 minutes	Intravenous	Dry mouth, pruritis
List T, Tegelberg A, Haraldson T, Isacsson G. Intra-articular morphine as analgesic in temporomandibular joint arthralgia/osteoarthritis. Pain 2001;94(3):275-282.	Chronic pain due to temporomandibular joint arthralgia/osteoarthritis	Morphine	0.1 or 1 mg	1 time	1 time treatment	Intra-articular injection	Headache, dizziness, vertigo
Ma K, Jiang W, Zhou Q, Du DP. The efficacy of oxycodone for management of acute pain episodes in chronic neck pain patients. Int J Clin Pract 2008;62(2):241-247.	Chronic neck pain	Oxycodone (controlled-release)	5 mg or 10 mg (initial dose) continued to 25–50% increase or decrease in dosage depending on effects on pain	2 times daily	2-4 weeks	Oral	Nausea, constipation, pruritus
Maier C, Hildebrandt J, Klinger R, Henrich-Eberl C, Lindena G. Morphine responsiveness, efficacy and tolerability in patients with chronic non-tumor associated pain - results of a double-blind placebo-controlled trial (MONTAS). Pain 2002;97(3):223-233.	Various chronic non-cancer pain conditions	Morphine (sustained-release)	20 mg (initial dose) titrated to 180 mg (maximum dose)	2 times daily	2 weeks	Oral	Nausea, sedation, dizziness
Malonne H, Coffiner M, Sonet B, Sereno A, Vanderbist F. Efficacy and tolerability of sustained-release tramadol in the treatment of symptomatic osteoarthritis of the hip or knee: a multicenter,	Chronic pain due to osteoarthritis (knee or hip)	Tramadol (sustained-release)	200 mg	1 time daily	14 days	Oral	Nausea, vomiting, somnolence

randomized, double-blind, placebo-controlled study. Clin Ther 2004;26(11):1774-1782.							
Mangel AW, Bornstein JD, Hamm LR, Buda J, Wang J, Irish W, Urso D. Clinical trial: asimadoline in the treatment of patients with irritable bowel syndrome. Aliment Pharmacol Ther 2008;28(2):239-249.	Irritable bowl syndrome	Asimadoline	0.15, 0.5, or 1.0 mg	2 times daily	12 weeks	Oral	Diarrhoea, abdominal pain, nausea
Martinetti L, Lodola E, Monafo V, Ferrari V. Clinical evaluation of an oral analgesic, Z.424, in patients with chronic pain. J Clin Pharmacol J New Drugs 1970;10(6):390-399.	Various chronic non-cancer pain conditions	Codeine	30 mg	Stage I: 2 capsules daily; stage II: 2 capsules, 3 times daily	Stage I: 3 days; stage II: 3 days	Oral	Nausea, vomiting
Matsumoto AK, Babul N, Ahdieh H. Oxymorphone extended-release tablets relieve moderate to severe pain and improve physical function in osteoarthritis: results of a randomized, double-blind, placebo- and active-controlled phase III trial. Pain Med 2005;6(5):357-366.	Chronic pain due to osteoarthritis (knee or hip)	Oxymorphone (extended-release) or oxycodone (controlled-release)	Oxymorphone (extended-release): 20 mg; 20 mg (initial dose) titrated to 40 mg; oxycodone (controlled-release): 10 mg (initial dose) titrated to 20 mg	2 times daily	4 weeks	Oral	Nausea, constipation, somnolence
Max MB, Byas-Smith MG, Gracely RH, Bennett GJ. Intravenous infusion of the NMDA antagonist, ketamine, in chronic posttraumatic pain with allodynia: a double-blind comparison to alfentanil and placebo. Clin Neuropharmacol 1995;18(4):360-368.	Chronic post-traumatic pain	Alfentanil	1.5 µg/kg/min; concentration was doubled at 60 min and 90 min, if inadequate pain relief	1 time daily	3 days	Intravenous	Sedation, nausea, dizziness
Max MB, Schafer SC, Culnane M, Dubner R, Gracely RH. Association of pain relief with drug side effects in postherpetic neuralgia: A single-dose study of clonidine, codeine, ibuprofen, and placebo. Clin Pharmacol Ther 1988;43(4):363-371.	Postherpetic neuralgia	Codeine	120 mg	1 time treatment	6 hours	Oral	Sleepiness, nauseated, light-headedness

Messick RT. Evaluation of acetaminophen, propoxyphene, and their combination in office practice. J Clin Pharmacol 1979;19(4):227-230.	Various chronic non-cancer pain conditions	Propoxyphene-alone or combination of acetaminophen / propoxyphene	Propoxyphene: 100 mg	1 tablet every 4-6 hours	2 days	Oral	Nausea, vomiting, dizziness
Morley JS, Bridson J, Nash TP, Miles JB, White S, Makin MK. Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. Palliat Med 2003;17(7):576-587.	Chronic neuropathic pain	Methadone	10 mg in the first 20 days and 20 mg in the last 28 days	1 time daily	48 days	Oral	Nausea, vomiting, somnolence
Morrison J, Ling F, Forman E, Bates G, Blake P, Vecchio T, Linden C, O'Connell M. Analgesic efficacy of ibuprofen for treatment of primary dysmenorrhea. South Med J 1980;73(8):999-1002.	Primary dysmenorrhoea	Propoxyphene	64 mg	2 tablets	3 times	Oral	None reported
Moulin DE, Iezzi A, Amireh R, Sharpe WK, Boyd D, Merskey H. Randomised trial of oral morphine for chronic non-cancer pain. Lancet 1996;347(8995):143-147.	Various chronic non-cancer pain conditions	Morphine (sustained-release)	Weekly graded doses of 15, 30, and 60 mg	2 times daily	3 weeks	Oral	Vomiting, dizziness, constipation
Munera C, Drehobl M, Sessler N, Landau C. A randomized, placebo-controlled, double-blinded, parallel-group, 5-week study of buprenorphine transdermal system in adults with osteoarthritis. J Opioid Manag 2009;6(3):193-202.	Chronic pain due to osteoarthritis	Buprenorphine	5 µg per hour (initial dose) titrated to 10 or 20 µg per hour as needed	1 patch lasting 72 hours	4 weeks	Transdermal patch	Nausea, vomiting, headache
Norrbrink C, Lundeberg T. Tramadol in neuropathic pain after spinal cord injury: a randomized, double-blind, placebo-controlled trial. Clin J Pain 2009;25(3):177-184.	Neuropathic pain after spinal cord injury	Tramadol	50 mg increased every 5 days by 50 mg until 400 mg	3 times daily	4 weeks	Oral	Tiredness, dry mouth, dizziness
Nuki G, Downie WW, Dick WC, Whaley K, Spooner JB, Darby-Dowman MA, Buchanan WW. Clinical trial of pentazocine in rheumatoid arthritis. Observations on the value of potent analgesics and placebos. Ann Rheum	Chronic pain due to rheumatoid arthritis	Pentazocine	25 mg	6 tablets daily	7 days	Oral	Dizziness, drowsiness, nausea

Dis 1973;32(5):436-443.							
O'Donnell J, Ekman E, Spalding W, Bhadra P, McCabe D, Berger M. The effectiveness of a weak opioid medication versus a cyclo-oxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drug in treating flare-up of chronic low-back pain: results from two randomized, double-blind, 6-week studies. J Int Med Res 2009;37(6):1789-1802.	Chronic low back pain	Tramadol	50 mg	4 times daily	6 weeks	Oral	Nausea, headache, dizziness
Park K-S, Choi J-J, Kim W-U, Min J-K, Park S-H, Cho C-S. The efficacy of tramadol/acetaminophen combination tablets (Ultracet®) as add-on and maintenance therapy in knee osteoarthritis pain inadequately controlled by nonsteroidal anti-inflammatory drug (NSAID). Clin Rheumatol 2012;31(2):317-323.	Chronic pain due to osteoarthritis	Combination of tramadol / acetaminophen	Tramadol: 37.5 mg	1 tablet (daily) for 3 days, then 1 tablet (2 times daily) for 4 days, 1 tablet (3 times daily) for 3 days, and thereafter as needed from 3-8 tablets daily	4 weeks	Oral	Nausea, dizziness, heartburn
Parr G, Darekar B, Fletcher A, Bulpitt C. Joint pain and quality of life; results of a randomised trial. Br J Clin Pharmacol 1989;27(2):235-242.	Chronic joint pain	Combination of dextropropoxyphene / paracetamol	Dextropropoxyphene: 180mg	Dextropropoxyphene: 2 tablets, 3 times daily	4 weeks	Oral	Central nervous system complaints, dizziness, tiredness
Pavelka K, Peliskova Z, Stehlikova H, Ratcliffe S, Repas C. Intraindividual differences in pain relief and functional improvement in osteoarthritis with diclofenac or tramadol. Clin Drug Investig 1998;16(6):421-429.	Chronic pain due to osteoarthritis (hip or knee)	Tramadol	50 mg	1-2 capsules, 3 times daily	4 weeks	Oral	Headache, nausea, constipation
Peloso PM, Bellamy N, Bensen W, Thomson GT, Harsanyi Z, Babul N, Darke AC. Double blind randomized placebo control trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. J	Chronic pain due to osteoarthritis (knee or hip)	Codeine (controlled-release)	100 mg (initial dose) escalated weekly to a maximum of 400 mg daily	1 time daily (initial dose) to 2 times daily	4 weeks	Oral	Constipation, somnolence, dizziness

Rheumatol 2000;27(3):764-771.							
Peloso PM, Fortin L, Beaulieu A, Kamin M, Rosenthal N. Analgesic efficacy and safety of tramadol/ acetaminophen combination tablets (Ultracet) in treatment of chronic low back pain: a multicenter, outpatient, randomized, double blind, placebo controlled trial. J Rheumatol 2004;31(12):2454-2463.	Chronic low back pain	Combination of tramadol / acetaminophen	37.5 mg	1 tablet (daily) to a maximum of 2 tablets (4 times daily) and a minimum of 3 tablets daily	91 days	Oral	Nausea, dizziness, constipation
Persson J, Hasselström J, Wiklund B, Heller A, Svensson JO, Gustafsson L. The analgesic effect of racemic ketamine in patients with chronic ischemic pain due to lower extremity arteriosclerosis obliterans. Acta Anaesthesiol Scand 1998;42(7):750-758.	Chronic ischemic lower extremity pain	Combination of ketamine / morphine	Morphine: 10 mg	1 time treatment	1 time treatment	Intravenous	Disturbed cognition/perception
Portenoy RK, Messina J, Xie F, Peppin J. Fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid-treated patients with chronic low back pain: a randomized, placebo-controlled study. Curr Med Res Opin 2007;23(1):223-233.	Chronic low back pain	Fentanyl	100 mg (initial dose) titrated to 200 or 400 or 600 of 800 µg (maximum dose)	At least 2 hours had to elapse before the next dose, and between subsequent doses.	3 weeks	Oral	Nausea, dizziness, somnolence
Price R, Latham A. Double-blind comparison of meptazinol (200 mg) and dextropropoxyphene /paracetamol in a multi-centre, general practice setting. Curr Med Res Opin 1982;8(1):54-60.	Various chronic pain conditions	Combination of d-propoxyphene / paracetamol	D-propoxyphene: 32.5 mg	2 tablets, 3-6 hours daily	14 days	Oral	Nausea, drowsiness, giddy/dizzy
Procacci P, Buzzelli G, Grazzini M, Monafo V. A controlled trial of a new analgesic (Z. 424) in experimental and pathological pain in comparison with codeine and aminopyrine. Curr	Various chronic pain conditions	Combination of parahydroxybenzoate / codeine	Codeine: 30 mg	1 capsule, 4 times daily	4 days	Oral	No side effects reported

Ther Res Clin Exp 1969;11(11):647-656.							
Quiding H, Grimstad J, Rusten K, Stubhaug A, Bremnes J, Breivik H. Ibuprofen plus codeine, ibuprofen, and placebo in a single- and multidose cross-over comparison for coxarthrosis pain. Pain 1992;50(3):303-307.	Coxarthrosis pain	Combination of ibuprofen / codeine	Codeine: 30 mg	6 times daily	1 day	Oral	Nausea, constipation, flatulence
Raja SN, Haythornthwaite JA, Pappagallo M, Clark MR, Travison TG, Sabeen S, Royall RM, Max MB. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2002;59(7):1015-1021.	Postherpetic neuralgia	Morphine (controlled-release) or methadone	Morphine (controlled-release): 15 mg; methadone: 91 mg	1-16 capsules daily, until pain relief	8 weeks	Oral	Constipation, nausea, dizziness
Rocco AG, Frank E, Kaul AF, Lipson SJ, Gallo JP. Epidural steroids, epidural morphine and epidural steroids combined with morphine in the treatment of post-laminectomy syndrome. Pain 1989;36(3):297-303.	Chronic pain due to post-laminectomy syndrome	Combination of lidocaine / morphine or combination of lidocaine / morphine / triamcinolone	Morphine: 8 mg	1 time monthly	3 months	Injection (epidural)	Urinary retention, nausea/vomiting, pruritus
Rooney GI. Successful use of a moderate analgesic (Fortagesic) in the symptomatic treatment of osteoarthritis. J Int Med Res 1979;7(1):77-82.	Chronic pain due to osteoarthritis	Combination of paracetamol / pentazocine	Pentazocine: 15 mg	2 tablets, 3 times daily	14 days	Oral	Gastrointestinal events
Roth SH, Fleischmann RM, Burch FX, Dietz F, Bockow B, Rapoport RJ, Rutstein J, Lacouture PG. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: placebo-controlled trial and long-term evaluation. Arch Intern Med 2000;160(6):853-860.	Chronic pain due to osteoarthritis	Oxycodone (controlled-release)	10 or 20 mg	2 times daily	14 days	Oral	Nausea, vomiting, somnolence

Roth SH. Efficacy and safety of tramadol HCl in breakthrough musculoskeletal pain attributed to osteoarthritis. J Rheumatol 1998;25(7):1358-1363.	Chronic pain due to osteoarthritis	Tramadol	50 mg/tablet	1-2 tablets every 4 to 6 hours	13 days	Oral	Nausea, drowsiness, vomiting
Rowbotham MC, Reisner-Keller LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia. Neurology 1991;41(7):1024-1028.	Postherpetic neuralgia	Morphine	Initial dose was infused at 0.3 mg/kg up to a maximum dose of 25 mg	1 time treatment	3 infusions, 3 times	Intravenous	Not reported
Ruoff GE, Rosenthal N, Jordan D, Karim R, Kamin M. Tramadol/acetaminophen combination tablets for the treatment of chronic lower back pain: a multicenter, randomized, double-blind, placebo-controlled outpatient study. Clin Ther 2003;25(4):1123-1141.	Chronic low back pain	Combination of tramadol / acetaminophen	37.5 mg	1 tablets daily to a maximum of 8 tablets daily	3 months	Oral	Nausea, somnolence, constipation
Ruoff GE. Slowing the initial titration rate of tramadol improves tolerability. Pharmacotherapy 1999;19(1):88-93.	Chronic joint pain	Tramadol	1-, 4-, 10-day titration to attain the study target dosage of 200mg daily	4 times daily	14 days	Oral	Gastrointestinal events dizziness, somnolence
Russell IJ, Kamin M, Bennett RM, Schnitzer TJ, Green JA, Katz WA. Efficacy of tramadol in treatment of pain in fibromyalgia. J Clin Rheumatol 2000;6(5):250-257.	Fibromyalgia	Tramadol	Initial dose was set according to the dose that provided stable pain control during the run-in phase (maximum dose of 400 mg)	1 time daily	6 weeks	Oral	Nausea, somnolence, dizziness
Salzman RT, Brobyn RD. Long-term comparison of suprofen and propoxyphene in patients with osteoarthritis. Pharmacology 1983;27 Suppl 1:55-64.	Chronic pain due to osteoarthritis	Propoxyphene	65 mg	4 times daily	24 weeks	Oral	Nausea, dizziness, headache
Schnitzer TJ, Gray WL, Paster RZ, Kamin M. Efficacy of tramadol in treatment of chronic low back pain. J Rheumatol 2000;27(3):772-778.	Chronic low back pain	Tramadol	Initial dose titrated to 200-400 mg	Not reported	4 weeks	Oral	Nausea, dizziness, somnolence

Schnitzer TJ, Kamin M, Olson WH. Tramadol allows reduction of naproxen dose among patients with naproxen-responsive osteoarthritis pain: a randomized, double-blind, placebo-controlled study. Arthritis Rheum 1999;42(7):1370-1377.	Chronic pain due to osteoarthritis	Tramadol	200 mg daily	1 time daily	13 weeks	Oral	Nausea, dizziness, vomiting
Schwartz S, Etropolski M, Shapiro DY, Okamoto A, Lange R, Haeussler J, Rauschkolb C. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin 2010;27(1):151-162.	Painful diabetic neuropathy	Tapentadol (extended-release)	Initial dose titrated to 100-250 mg	2 times daily	12 weeks	Oral	Nausea, diarrhea, anxiety
Scopa J, Jorgensen PB, Foster JB. Migraleve in the prophylaxis of migraine. Curr Ther Res Clin Exp 1974;16(12):1270-1275.	Migraine	Combination of buclizine dihydrochloride / paracetamol / codeine / dioctyl sodium sulphosuccinate	Codeine: 8 mg	2 tablets, every other day	3 months	Oral	Tiredness, weight gain, slight depression
Sedgwick J, Daily H, Langrick A, Hill R. Double-blind study of meptazinol, D-propoxyphene/paracetamol and placebo in patients with primary dysmenorrhoea. Current therapeutic research 1985;38(3):528-535.	Primary dysmenorrhoea	Combination of d-propoxyphene / paracetamol	D-propoxyphene: 65 mg	2 tablets	3 times	Oral	Nausea, dizziness, headache
Sheather-Reid RB, Cohen M. Efficacy of analgesics in chronic pain: a series of N-of-1 studies. J Pain Symptom Manage 1998;15(4):244-252.	Cervicobrachial pain syndrome or fibromyalgia	Codeine	30 mg	4 times daily	12 weeks	Oral	Constipation, headache, dry mouth
Siddall PJ, Molloy AR, Walker S, Mather LE, Rutkowski SB, Cousins MJ. The efficacy of intrathecal morphine and clonidine in the treatment of pain after spinal cord injury. Anesth Analg 2000;91(6):1493-1498.	Chronic neuropathic pain	Morphine-alone or combination of morphine / clonidine	0.2 to 1 mg (initial dose) increased by 1.5 times on 2nd day and by 2 times on 3rd day, if inadequate pain relief; after administration of morphine attainment of either satisfactory pain relief or	1 time daily	6 days	Intrathecal injection	Hypotension, nausea, sedation

			side effects, participants received a mixture of morphine (half of final dose from previous stage)				
Silverfield JC, Kamin M, Wu SC, Rosenthal N. Tramadol/acetaminophen combination tablets for the treatment of osteoarthritis flare pain: a multicenter, outpatient, randomized, double-blind, placebo-controlled, parallel-group, add-on study. Clin Ther 2002;24(2):282-297.	Chronic pain due to osteoarthritis (knee or hip)	Combination of tramadol / acetaminophen	37.5 mg or 75 mg	1 or 2 tablets (of combination treatment) daily	10 days	Oral	Nausea, dizziness, vomiting
Simpson DM, Messina J, Xie F, Hale M. Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a multicenter, randomized, double-blind, placebo-controlled study. Clin Ther 2007;29(4):588-601.	Chronic non-cancer neuropathic pain	Fentanyl	100 mg (initial dose) titrated to 200 or 400 or 600 of 800 µg (maximum dose)	Every 2 hours, as needed	21 days	Oral	Nausea, vomiting, somnolence
Sindrup SH, Andersen G, Madsen C, Smith T, Brosen K, Jensen TS. Tramadol relieves pain and allodynia in polyneuropathy: a randomised, double-blind, controlled trial. Pain 1999;83(1):85-90.	Polyneuropathy	Tramadol (slow-release)	Initial dose titrated to at least 200 mg daily and at highest 400 mg daily	2 times daily	4 weeks	Oral	Tiredness, dizziness, dry mouth
Somerville BW. Treatment of migraine attacks with an analgesic combination (Mersyndol). Med J Aust 1976;1(23):865-866.	Migraine	Combination of paracetamol / codeine / doxylamine succinate	Codeine: 9.75 mg	2 tablets (initial dose) increased to 2 tablets every 4 hours daily	3 weeks	Oral	Drowsiness
Sorensen J, Bengtsson A, Ahlner J, Henriksson KG, Ekselius L, Bengtsson M. Fibromyalgia--are there different mechanisms in the processing of pain? A double blind crossover comparison of analgesic drugs. J Rheumatol 1997;24(8):1615-1621.	Fibromyalgia	Morphine	0.3 mg/kg	1 time treatment	30 minutes	Intravenous	Sedation, nausea/emesis, pruritus

Sorge J, Sittl R. Transdermal buprenorphine in the treatment of chronic pain: Resultsof a phase III, multicenter, randomized, double-blind, placebo-controlled study. Clin Ther 2004;26(11):1808-1820.	Various chronic pain conditions	Buprenorphine	35 µg	3 sequential patches lasting 72 hours	15 days	Transdermal patch	Nausea, dizziness, vomiting
Spacek A, Böhm D, Kress H-G. Ganglionic local opioid analgesia for refractory trigeminal neuralgia. The Lancet 1997;349(9064):1521.	Trigeminal neuralgia	Buprenorphine	0.045 mg in 1.5 mL 0.9% NaCl	1 injection, 1 time daily	5 days	Intravenous	No side effects reported
Staquet M, Luyckx A, Cauwenberge H. A Double-Blind Comparison of Alclofenac, Pentazocine, and Codeine with Placebo Control in Pathologic Pain. The Journal of clinical pharmacology and new drugs 1971;11(6):450-455.	Chronic pathological pain	Trial I: Codeine Trial II: Pentazocine	Trial I: Codeine: 30 mg Trial II: Pentazocine: 50 mg	3 times	6 hours	Oral	Dyspepsia, drowsiness
Stein A, Yassouridis A, Szopko C, Helmke K, Stein C. Intraarticular morphine versus dexamethasone in chronic arthritis. Pain 1999;83(3):525-532.	Chronic pain due to arthritis	Morphine	3 mg	1 time treatment	1 treatment	Intra-articular injection	No side effects reported
Steiner DJ, Sitar S, Wen W, Sawyerr G, Munera C, Ripa SR, Landau C. Efficacy and safety of the seven-day buprenorphine transdermal system in opioid-naive patients with moderate to severe chronic low back pain: an enriched, randomized, double-blind, placebo-controlled study. J Pain Symptom Manage 2011;42(6):903-917.	Chronic low back pain	Buprenorphine	10 µg per hour (initial dose) titrated to 20 µg per hour as needed	1 patch lasting 7 days	84 days	Transdermal patch	Nausea, vomiting, constipation
Stiell IG, Dufour DG, Moher D, Yen M, Beilby WJ, Smith NA. Methotrimeprazine versus meperidine and dimenhydrinate in the treatment of severe migraine: a randomized, controlled trial. Ann Emerg Med	Migraine	Combination of meperidine / dimenhydrinate	Meperidine: 75 mg	1 time treatment	1 hour	Injection (intramuscular)	Nausea/vomiting, dizziness, drowsiness

1991;20(11):1201-1205.							
Szarka LA, Camilleri M, Burton D, Fox JC, McKinzie S, Stanislav T, Simonson J, Sullivan N, Zinsmeister AR. Efficacy of on-demand asimadoline, a peripheral kappa-opioid agonist, in females with irritable bowel syndrome. Clin Gastroenterol Hepatol 2007;5(11):1268-1275.	Irritable Bowel Syndrome	Asimadoline	0.5 (initial dose) up to 1 mg as necessary	4 times daily	4 weeks	Oral	Adverse events related to central and peripheral nervous system, respiratory, gastrointestinal
Thorne C, Beaulieu AD, Callaghan DJ, O'Mahony WF, Bartlett JM, Knight R, Kraag GR, Akhras R, Piraino PS, Eisenhoffer J, Harsanyi Z, Darke AC. A randomized, double-blind, crossover comparison of the efficacy and safety of oral controlled-release tramadol and placebo in patients with painful osteoarthritis. Pain Res Manag 2008;13(2):93-102.	Chronic pain due to osteoarthritis	Tramadol (controlled-release)	150 mg (initial dose) titrated weekly to 200, 300, 400 mg (maximum dose)	1 time daily	8 weeks	Oral	Nausea, constipation, sweating
Turhanoglu AD, Guler H, Inanoglu D, Inanoglu K, Turhanoglu S. Tramadol iontophoresis added to treatment of knee osteoarthritis. Turk J Rheumatol 2010; 25: 174-8.	Chronic pain due to osteoarthritis (knee)	Tramadol	1 mL	10 sessions	2 weeks	Intravenous injection followed by iontophoresis	Nausea, vomiting, constipation
Vernassiere C, Cornet C, Trechot P, Alla F, Truchetet F, Cuny JF, Commun N, Granel Brocard F, Barbaud A, Schmutz JL. Study to determine the efficacy of topical morphine on painful chronic skin ulcers. J Wound Care 2005;14(6):289-293.	Painful chronic skin ulcers	Morphine	10 mg	1 time daily	5 days	Topical	Constipation
Vlok GJ, van Vuren JP. Comparison of a standard ibuprofen treatment regimen with a new ibuprofen/paracetamol/codeine combination in	Chronic pain due to osteoarthritis	Combination of ibuprofen / paracetamol / codeine	Codeine: 10 mg	2 tablets, 3 times daily	56 days	Oral	Constipation, nausea, abdominal discomfort

chronic osteo-arthritis. S Afr Med J 1987;Suppl:1, 4-6.							
Vojtassak J, Vojtassak J, Jacobs A, Rynn L, Waechter S, Richarz U. A Phase IIIb, Multicentre, Randomised, Parallel-Group, Placebo-Controlled, Double-Blind Study to Investigate the Efficacy and Safety of OROS Hydromorphone in Subjects with Moderate-to-Severe Chronic Pain Induced by Osteoarthritis of the Hip or the Knee. Pain research and treatment 2011;2011:239501.	Chronic pain due to osteoarthritis	Hydromorphone	4 mg	1 time daily	16 weeks	Oral	Nausea, constipation
Vondrackova D, Leyendecker P, Meissner W, Hopp M, Szombati I, Hermanns K, Ruckes C, Weber S, Grothe B, Fleischer W, Reimer K. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. J Pain 2008;9(12):1144-1154.	Chronic non-malignant low back pain	Combination of oxycodone (prolonged-release) / naloxone (prolonged-release)	10/5 mg or 20/10 mg	2 times daily	12 weeks	Oral	Constipation, nausea, headache
Vorsanger GJ, Xiang J, Gana TJ, Pascual ML, Fleming RR. Extended-release tramadol (tramadol ER) in the treatment of chronic low back pain. Journal of opioid management 2008;4(2):87-97.	Chronic low back pain	Tramadol (extended-release)	200, or 300 mg	1 time daily	12 weeks	Oral	Nausea, constipation, headache
Wallace MS, Moulin D, Clark AJ, Wasserman R, Neale A, Morley-Forster P, Castaigne JP, Teichman S. A Phase II, multicenter, randomized, double-blind, placebo-controlled crossover study of CJC-1008--a long-acting, parenteral opioid analgesic--in the treatment of postherpetic neuralgia. Journal of opioid management 2006;2(3):167-173.	Postherpetic neuralgia	Modification of Dynorphin A	Not reported	1 time treatment	30 minutes	Intravenous	Pain, erythema, burning

Wallace W, Elliott C, Price V. A combination of ibuprofen and codeine phosphate provides superior analgesia to ibuprofen alone in osteoarthritis. BRITISH JOURNAL OF CLINICAL RESEARCH 1994;5.	Chronic pain due to osteoarthritis (hip or knee)	Phase I: Codeine-alone or combination of ibuprofen / codeine Phase II: Combination of ibuprofen / codeine	Codeine: 12.5 mg (both phases)	Phase I: 2 tablets, 1 time daily Phase II: 2 tablets, 4 times daily	Phase I: 4 days Phase II: 1 week	Oral	Constipation, drowsiness, upper gastrointestinal events
Wasan AD, Davar G, Jamison R. The association between negative affect and opioid analgesia in patients with discogenic low back pain. Pain 2005;117(3):450-461.	Chronic low back pain	Morphine	0.075 mg/kg ideal body weight	2 infusions sessions	1 time treatment	Intravenous	Not reported
Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. Neurology 1998;50(6):1837-1841.	Postherpetic neuralgia	Oxycodone (controlled-release)	10 mg (initial dose) escalated to 60 mg (maximum dose)	2 times daily	4 weeks	Oral	Constipation, sedation, nausea
Watson CP, Moulin D, Watt-Watson J, Gordon A, Eisenhoffer J. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. Pain 2003;105(1-2):71-78.	Painful diabetic neuropathy	Oxycodone (controlled-release)	10 mg (initial dose) titrated to 20 to 30 to 40 mg every 2-7 days	2 times daily	4 weeks	Oral	Nausea, somnolence, constipation
Webster LR, Butera PG, Moran LV, Wu N, Burns LH, Friedmann N. Oxytrex minimizes physical dependence while providing effective analgesia: a randomized controlled trial in low back pain. J Pain 2006;7(12):937-946.	Chronic low back pain	Combination of oxycodone / ultralow-dose naltrexone or oxycodone alone	Oxycodone: 10 mg/day (initial dose) titrated to 20, 30, 40, 60, and 80 mg/day (maximum dose)	Combination treatment: 2 times or 4 times daily; oxycodone alone: 4 times daily	12 weeks	Oral	Constipation, dizziness, somnolence
Wu CL, Agarwal S, Tella PK, Klick B, Clark MR, Haythornthwaite JA, Max MB, Raja SN. Morphine versus mexiletine for treatment of postamputation pain: a randomized, placebo-controlled, crossover trial. Anesthesiology 2008;109(2):289-296.	Chronic post-amputation pain	Morphine (sustained-release)	15 mg	1 time daily	8 weeks	Oral	Constipation, nausea, drowsiness
Zin CS, Nissen LM, O'Callaghan JP, Duffull SB, Smith MT, Moore BJ. A randomized, controlled trial of oxycodone versus placebo in patients	Postherpetic neuralgia and painful diabetic neuropathy	Oxycodone (controlled-release)	10 mg	2 times daily	5 weeks	Oral	Dizziness, drowsiness, constipation

with postherpetic neuralgia and painful diabetic neuropathy treated with pregabalin. The Journal of Pain 2010;11(5):462-471.							

eTable 2. Reporting of patient-important outcome domains in protocols and papers of eligible studies

Study		IMMPACT-recommended patient-important outcome domain								
		Pain	Physical functioning	Emotional functioning	Participant ratings of global improvement and	Symptoms and adverse events	Participant disposition	Role functioning	Interpersonal functioning	Sleep and fatigue
1	Protocol	+	+	+	-	+	N/A	-	-	+
	Paper	+	+	+	-	+	+	+	-	+
2	Protocol	+	-	-	-	-	N/A	-	-	+
	Paper	+	+	+	+	+	+	+	-	+
3	Protocol	+	-	-	-	+	N/A	-	-	-
	Paper	+	-	-	+	+	+	-	-	-
4	Protocol	+	-	-	-	-	N/A	-	-	-
	Paper	+	-	-	-	+	+	-	-	-
5	Protocol	+	-	-	-	-	N/A	-	-	-
	Paper	+	-	-	+	+	+	-	-	-
6	Protocol	+	-	-	+	-	N/A	-	-	+
	Paper	+	+	+	+	+	+	+	-	+
7	Protocol	+	+	-	+	-	N/A	-	-	+
	Paper	+	+	+	+	+	+	+	-	+
8	Protocol	+	+	-	-	+	N/A	-	-	+
	Paper	+	+	+	+	+	+	+	+	+
9	Protocol	+	-	-	-	+	N/A	-	-	+
	Paper	+	+	+	+	+	+	-	-	+
10	Protocol	+	-	-	-	+	N/A	-	-	-
	Paper	+	-	-	-	+	+	-	-	-
11	Protocol	+	-	-	+	+	N/A	-	-	+
	Paper	+	-	-	+	+	+	-	-	-
12	Protocol	+	+	-	-	-	N/A	-	-	-
	Paper	+	+	-	-	+	+	-	-	-
13	Protocol	+	-	-	-	-	N/A	-	-	-
	Paper	+	-	-	+	+	+	-	-	-
14	Protocol	-	-	-	-	-	N/A	-	-	-
	Paper	+	-	-	-	-	+	-	-	-

(+) presence of outcome domain and (-) absence of outcome domain; pairs of yellow boxes indicate no change in reporting of outcome domain from protocol, pairs of green boxes indicate addition in reporting of outcome domain to protocol, pairs of red boxes indicate deletion in reporting of outcome domain from protocol; N/A = not applicable (participant disposition is only applicable to papers)

CHAPTER 3

At the time of writing this thesis, this chapter has been accepted for publication in a peer-reviewed scientific journal, as follows:

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Management of central post-stroke pain: a systematic review of randomized controlled trials

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List of tables and figures: Tables 1, 2; Figures 1, 2, 3, 4A/4B

Key words: central post-stroke pain; systematic reviews; neuropathic pain; clinical epidemiology; evidence-based medicine; clinical trials.

Subject codes: [27] Other Treatment, [83] Other Stroke

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Abstract

Background and purpose: Central post-stroke pain (CPSP) is a chronic neuropathic disorder that follows a stroke. Current research on its management is limited, and no review has evaluated all therapies for CPSP.

Methods: We conducted a systematic review of randomized controlled trials (RCTs) to evaluate therapies for CPSP. We identified eligible trials, in any language, by systematic searches of AMED, CENTRAL, CINAHL, DARE, EMBASE, HealthSTAR, MEDLINE, and PsychINFO. Eligible trials: (1) enrolled ≥10 patients with CPSP; (2) randomly assigned them to an active therapy or a control arm; and, (3) collected outcome data ≥14 days after treatment. Pairs of reviewers, independently and in duplicate, screened titles and abstracts of identified citations, reviewed full texts of potentially eligible trials, and extracted information from eligible studies. We used a modified Cochrane tool to evaluate risk of bias of eligible studies, and collected patient-important outcomes according to recommendations by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials. We conducted, when possible, random-effects meta-analyses, and evaluated our certainty in treatment effects using the Grading of Recommendations Assessment, Development and Evaluation system.

Results: Eight eligible English-language RCTs (459 patients) tested anticonvulsants, an antidepressant, an opioid antagonist, repetitive transcranial magnetic stimulation, and acupuncture. Results suggested that all therapies had little to no effect on pain and other patient-important outcomes. Our certainty in the treatment estimates ranged from very low to low.

Conclusions: Our findings are inconsistent with major clinical practice guidelines; the available evidence suggests no beneficial effects of any therapies that researchers have evaluated in RCTs.

Introduction

Central post-stroke pain (CPSP) is a chronic (≥3 months) neuropathic disorder that can occur after a lesion or disease affecting the central somatosensory system.[1] The pain may be spontaneous, occurring either constantly or intermittently, or evoked in response to external stimuli.[1] It may develop immediately after a stroke, or years later.[2-5] To date, the largest prospective study, which enrolled 15,754 participants with ischemic stroke from 35 countries, found that 2.7% of patients developed CPSP at one year after stroke.[6] Because CPSP case definition is complex,[1] however, its reported prevalence is variable, and dependant of the site of lesion: one study, for instance, found that 25% of patients with brainstem infarcts developed CPSP within six months.[4] Individuals with CPSP commonly experience sensory abnormalities, including increased tactile and thermal sensitivities, which impair their quality of life.[7-9] The underlying mechanisms of CPSP are poorly understood,[1] contributing to challenges in its management.

There are several pharmacological and non-pharmacological therapies available for patients with CPSP; few systematic reviews have, however, summarized their effectiveness and safety.[10-12] The available reviews suffer from important limitations,[13] including the following: (1) limited strategies to identify relevant studies, including using few search terms, omitting major literature databases,

and excluding non-English language studies; (2) limited safeguards against misleading results, including failure to conduct study selection, risk of bias assessment, and data extraction in duplicate; or, (3) focusing on specific types of therapies, i.e. either pharmacological or non-pharmacological. As well, none of the reviews evaluated treatment effects on patient-important outcomes beyond pain and adverse events, quantitatively synthesized results using meta-analytic techniques, or used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate certainty in the evidence.[14]

We conducted a systematic review that addresses the limitations of prior reviews to inform evidence-based management of CPSP.

Methods

Standardized reporting

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews of randomized controlled trials (RCTs).[15]

Protocol registration

We registered our protocol with PROSPERO (registration number: CRD42014007189).

Literature search

We searched for relevant studies, in any language, by tailored searches of AMED, CENTRAL, CINAHL, DARE, EMBASE, HealthSTAR, MEDLINE, and PsychINFO, from the inception of each database through December, 2013. An experienced academic librarian developed the search strategy for each electronic database (for our search strategy for MEDLINE, please see Online Supplement).

Eligibility criteria

Eligible trials: (1) enrolled ≥10 patients with CPSP; (2) randomly assigned them to a therapeutic intervention (pharmacological or non-pharmacological) or a control arm; and, (3) collected outcome data ≥14 days after treatment. If a

study enrolled a mixed clinical population, we followed a systematic approach (Supplemental Figure I) to determine its eligibility. Ultimately, we included such studies if they met the above criteria, and if: (1) the authors provided the results separately for the participants with CPSP; or, failing that, (2) at least 80% of a study's sample comprised participants with CPSP.

We excluded trials that enrolled <10 CPSP patients due to the very limited information that we would gain from such studies, and we excluded trials with <2 week follow-up as patients with chronic pain will have little interest in short-acting treatment effects.[16]

Study selection

Teams of reviewers worked independently and in duplicate to determine eligibility status of all identified citations, first by screening the titles and abstracts, then by reviewing the full texts of all potential eligible articles. Reviewers resolved any disagreements by discussion, or with the help of an adjudicator. We recruited reviewers proficient in the relevant languages to review the full texts of all non-English studies. At this stage, we measured chance-independent agreement (Φ) – which has several advantages over traditional approaches (e.g. kappa), including less vulnerability to unequal distributions of results – and interpreted results using established criteria.[17] We used an online systematic review software application (DistillerSR™, Evidence

Partners, Ottawa, Canada; http://systematic-review.net/) to facilitate screening.

Data extraction

Reviewers used a pilot-tested, standardized form to extract information from each eligible study, including participant demographics, treatment details, study methodology, and outcome data as guided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT). Specifically, we collected outcome data, when available, across the following IMMPACT-recommended patient-important domains: (1) pain; (2) physical functioning; (3) emotional functioning; (4) participant ratings of global improvement and satisfaction with treatment; (5) symptoms and adverse events; (6) participant disposition; (7) role functioning; (8) interpersonal functioning; and, (9) sleep and fatigue.[18, 19] Reviewers resolved any disagreements by discussion, or with the help of an adjudicator.

Risk of bias assessment

Reviewers assessed risk of bias for each eligible study using a modified Cochrane risk of bias instrument that includes response options of "definitely or probably yes" – assigned a low risk of bias – or "definitely or probably no" – assigned a high risk of bias – an approach that we have previously validated.[20] Specifically, we evaluated random sequence generation, allocation

concealment, blinding of participants and study personnel, and incomplete outcome data.

Meta-analyses

When possible, we conducted meta-analyses using random-effects models that are conservative in that they consider both within- and between-study variability. We used the means and associated standard deviations (SDs) of the scores from the longest follow-up time-point in each study for our pooled analyses. If a study only reported a median score and a corresponding interquartile range (IQR), we assumed the mean score to be equal to the median, and calculated the SD to be equal to the IQR divided by 1.35.[21] If investigators used more than one instrument within a trial to measure the same construct, we chose a single measure as guided by the following prioritization, in descending order of importance: (1) most commonly used instrument; (2) instrument with the strongest evidence of validity; or, (3) instrument with the most precise estimation of effect. In our analyses, we treated data from crossover trials as if they were from parallel trials.[21]

Facilitating interpretation of results

For studies that provided binary outcome measures, we calculated relative risks (RRs) and the associated 95% confidence intervals (CIs) to inform relative effectiveness of treatments. For any pooled comparisons that suggested a

statistically significant treatment effect, we planned to generate associated measures of absolute effect, i.e. risk differences and numbers needed to treat.

When pooling continuous outcomes in which studies used the same instrument, we planned to calculate the weighted mean difference (WMD), which maintains the original unit of measurement and represents the average difference between groups. For trials that used different continuous outcome measures that addressed the same construct, we converted all instruments to the most commonly used outcome measure among studies, then pooled results using the WMD.[22] For any pooled comparisons that suggested a statistically significant treatment effect, we planned to calculate the proportion of participants who benefited, i.e. demonstrated improvement greater than or equal to the minimally important difference in each trial, then aggregate the results across all studies, and generate measures of relative and absolute treatment effects. For studies that reported effects of therapies on reducing pain, we also planned to use thresholds of ≥20%, ≥30% and ≥50% improvement from baseline to optimize interpretation of treatment effects.[16]

Assessment of heterogeneity and subgroup analyses

For each pooled analysis, we examined heterogeneity using both the chi-squared test and the I^2 statistic, which represents the percentage of variability

that is due to true differences between studies (heterogeneity) rather than sampling error (chance).[23]

We generated six *a priori* hypotheses to explain variability between studies: (1) interventions will show larger effects in trials that excluded participants in receipt of disability benefits or involved in litigation versus trials that included such participants;[24] (2) interventions will show smaller effects among trials with longer follow-up times versus trials with shorter follow-up times; (3) interventions will show smaller effects among trials enrolling participants with psychiatric co-morbidities versus trials that do not; (4) interventions will show smaller effects among trials enrolling participants with longer duration of CPSP prior to therapy versus trials that enrol participants with shorter duration of CPSP; (5) interventions will show larger effects in trials testing them at higher doses versus trials testing them at lower doses; and, (6) interventions will show larger effects in trials with greater risk of bias versus trials with lower risk of bias. We planned to conduct this last subgroup analysis on a risk of bias component-by-component basis, only if there was considerable variability within the risk of bias component. We planned to conduct tests of interaction to establish if the effect size from the subgroups differed significantly from each other.[25] We did not conduct subgroup analyses if there were fewer than three studies in a given subgroup.

Certainty in treatment estimates

We used the GRADE approach to categorize certainty in effect estimates for all reported outcomes as high, moderate, low, or very low.[14] Using this approach, RCTs begin as high certainty but can be rated down due to: (1) risk of bias;[26] (2) inconsistency;[27] (3) indirectness;[28] (4) imprecision;[29] and, (5) publication bias.[30] For any pooled comparisons that suggested a statistically significant treatment effect, we planned to use recent approaches to address missing participant data for binary and continuous outcomes.[31-33] When plausible worst-case scenarios reversed treatment effects, we planned to rate down for risk of bias. We presented our results in GRADE evidence profiles.[34-36]

Analytical software

We conducted meta-analyses using Review Manager (RevMan), version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We rated our certainty in effect estimates and created GRADE evidence profiles using GRADEproGDT (http://www.guidelinedevelopment.org/).

Results

We identified 5,015 unique records, of which we retrieved 324 in full text (Figure 1). After reviewing the full texts, we deemed eight English-language studies that enrolled 459 patients with CPSP eligible for our review (Table 1).[37-44] There was almost perfect agreement ($\Phi = 0.82$) between reviewers at the full-text review stage. All trials evaluated treatment effects on pain, and none reported effects on physical functioning, role functioning, or interpersonal functioning (Figure 2). The longest follow-up among eligible studies ranged from two to 12 weeks. No study reported the number of participants that were receiving disability benefits or were involved in litigation during the study period. One study reported no difference in the number of participants (in the pregabalin and placebo groups) who presented with psychiatric co-morbidities, specifically depression and insomnia.[41] Figure 3 portrays the risk of bias assessment.

Effects of pharmacotherapy on patient-important outcomes

Anticonvulsants

Very low certainty evidence from four trials (Table 2), which enrolled a total of 307 participants,[37, 40-42] showed that, when compared with placebo, anticonvulsants did not significantly reduce pain intensity (WMD on an 11-step scale: -0.75; 95% CI: -1.71 to 0.21; $I^2 = 69\%$) (Figure 4A), or increase adverse

events (RR: 1.61; 95% CI: 0.90 to 2.88; I^2 = 80%) (Figure 4B). Due to the small number of studies in each meta-analysis, and in line with our *a priori* criteria, we did not conduct our pre-specified subgroup analyses to explain inconsistency in results.

Low certainty evidence from three studies evaluated the effects of anticonvulsants on emotional functioning, most commonly in context of managing depression.[37, 41, 42] None reported a significant effect; variability in the presentation of the data precluded statistical pooling. Low certainty evidence from one study found that pregabalin (versus placebo) did not affect patient-reported global improvement, but did improve sleep (difference between least-squares means: -4.2, 95% CI: -8.4 to 0.0, p=0.049) (Table 2).

Tricyclic antidepressants

Low certainty evidence (Supplemental Table I) from one trial of 15 participants reported that, when compared with placebo, amitriptyline significantly reduced pain intensity during the last (fourth) week of treatment, although our reanalysis of the data did not find a significant effect.[37] The authors also reported that amitriptyline did not affect depressive symptoms, and was associated with significantly more adverse events than placebo (RR: 2.00, 95% CI: 1.15 to 3.49).

Opioid antagonists

Low certainty evidence (Supplemental Table II) from one trial of 20 participants reported that naloxone had no effect on pain when compared with placebo.[38]

Effects of non-pharmacotherapy on patient-important outcomes

Repetitive transcranial magnetic stimulation (rTMS)

Low certainty evidence (Supplemental Table III) from one trial (n=52) of rTMS versus sham stimulation found no significant differences in adverse events, depressive symptoms, or patient-reported global improvement.[43]

Acupuncture

Low certainty evidence (Supplemental Table IV) from one study (n=20) reported a significant effect of apipuncture over saline acupuncture for pain reduction (median 100-point Visual Analogue Scale score decrease: 36.50 versus 11.50, p=0.009).[44] Very low certainty evidence (Supplemental Table V) from another study (n=60) found no significant effect of electroacupuncture versus carbamazepine on a composite measure of joint pain, dysfunction, and tenderness.[39]

Discussion

Our systematic review found low or very low certainty evidence suggesting that anticonvulsants, tricyclic antidepressants, opioid antagonists, and electroacupuncture have no effect on reducing pain associated with CPSP. Low certainty evidence suggests that apipuncture may reduce pain, anticonvulsants may improve sleep, rTMS has no effect on depressive symptoms or patient-reported global improvement, and tricyclic antidepressants do not improve depressive symptoms and produce significantly more side effects.

Strengths and limitations

Our review has several strengths. First, we reviewed all non-pharmacological and pharmacological therapies for managing patients with CPSP. Second, we explored a wider range of literature databases than previous reviews, and searched for eligible studies in all languages. Third, teams of reviewers, who worked independently and in duplicate, made all subjective decisions, including study selection, risk of bias assessment, and data extraction. Fourth, we followed a systematic approach, which included working with expert clinicians and contacting study authors, to assess the eligibility of studies that enrolled mixed clinical populations. Fifth, we collected all patient-important outcomes across IMMPACT-recommended core outcome domains. Finally, we used the GRADE approach to evaluate our certainty in the evidence, and

presented our findings with GRADE evidence profiles. Our findings, however, are limited by shortcomings of the primary studies that were eligible for our review. This led to our ratings of low or very low certainty for all treatment effects.

Implications

Our findings are inconsistent with clinical practice guidelines by three major professional groups – the International Association for the Study of Pain Neuropathic Pain Special Interest Group, the European Federation of Neurological Societies (EFNS), and the Canadian Pain Society (CPS) – all of whom recommend tricyclic antidepressants as first-line therapy for managing patients with CPSP.[45-47] These recommendations are due to one trial of 15 participants that concluded that amitriptyline significantly reduced pain intensity versus placebo after four weeks of treatment.[37] Follow-up scores on the 10-step scale for pain, however, were very similar for amitriptyline (mean: 4.2; SD: 1.6) and placebo (mean: 5.3; SD: 2.0), and our re-analysis of the data found no significant effect (p=0.11).

The EFNS and CPS also recommend anticonvulsants as first-line pharmacological treatment for CPSP;[45, 46] our review found no evidence that they reduce pain. The EFNS, however, formulated its recommendations on the success of anticonvulsants in patients with other chronic neuropathic pain conditions. This

assumes that treatment responses are consistent across chronic neuropathic pain conditions. A recent systematic review provides some support for this assumption,[48] and we are further validating this hypothesis in an ongoing network meta-analysis of all therapies for all chronic neuropathic pain conditions.[49]

In the face of only low, or in most cases very low, certainty evidence, with initial evidence providing minimal or no support for benefit, management of CPSP remains extremely challenging. Investigators should mount large, multi-center, randomized trials using standardized instruments with known, satisfactory measurement properties to assess patient-important outcomes, including function. Such trials should include longer observation, and should implement strategies to reduce risk of bias, including generating the randomization sequence, concealing treatment allocation, and implementing strategies to minimize loss to follow-up. Given results thus far, such trials should evaluate both existing and innovative therapeutic options.

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Conflict(s)-of-Interest/Disclosure(s)

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Figure 1. Study flow chart

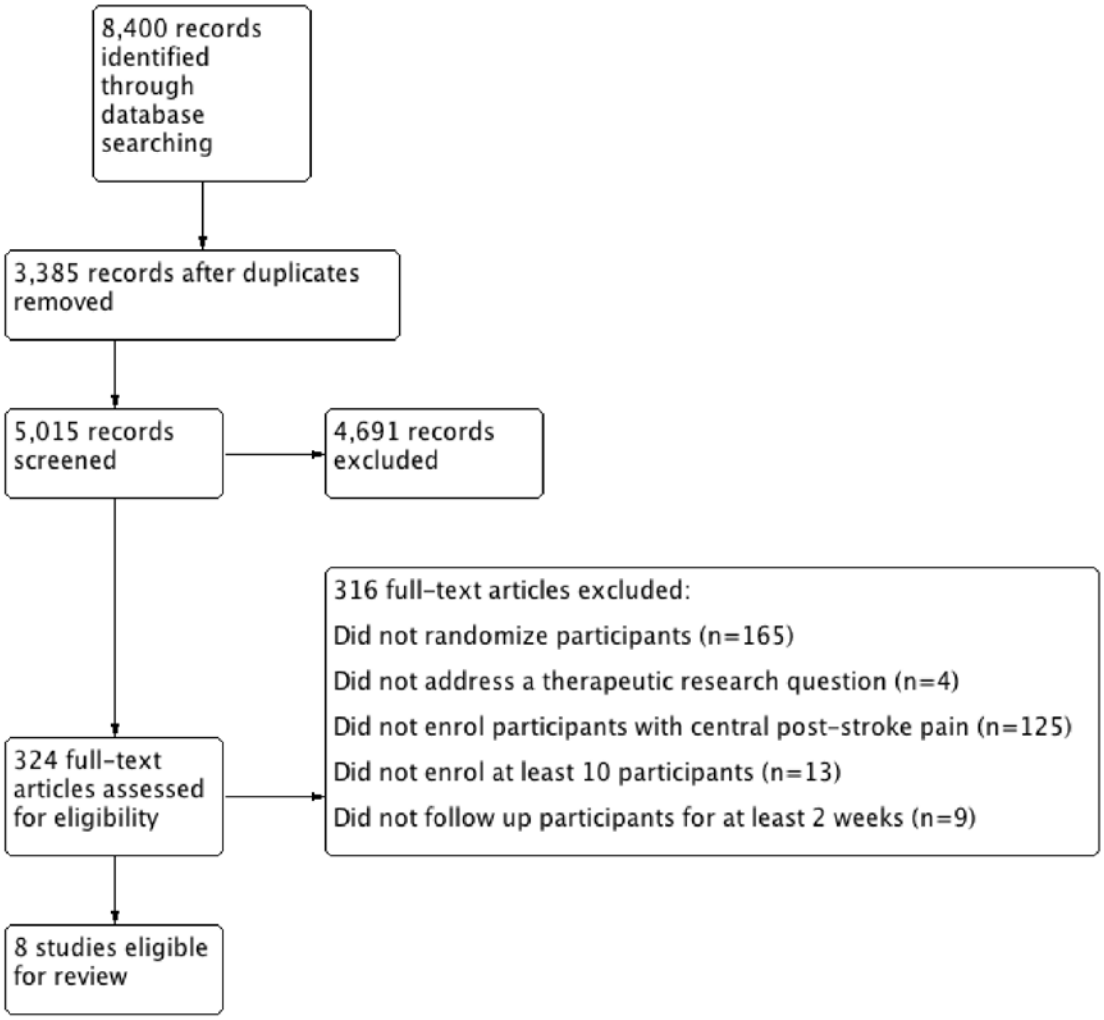
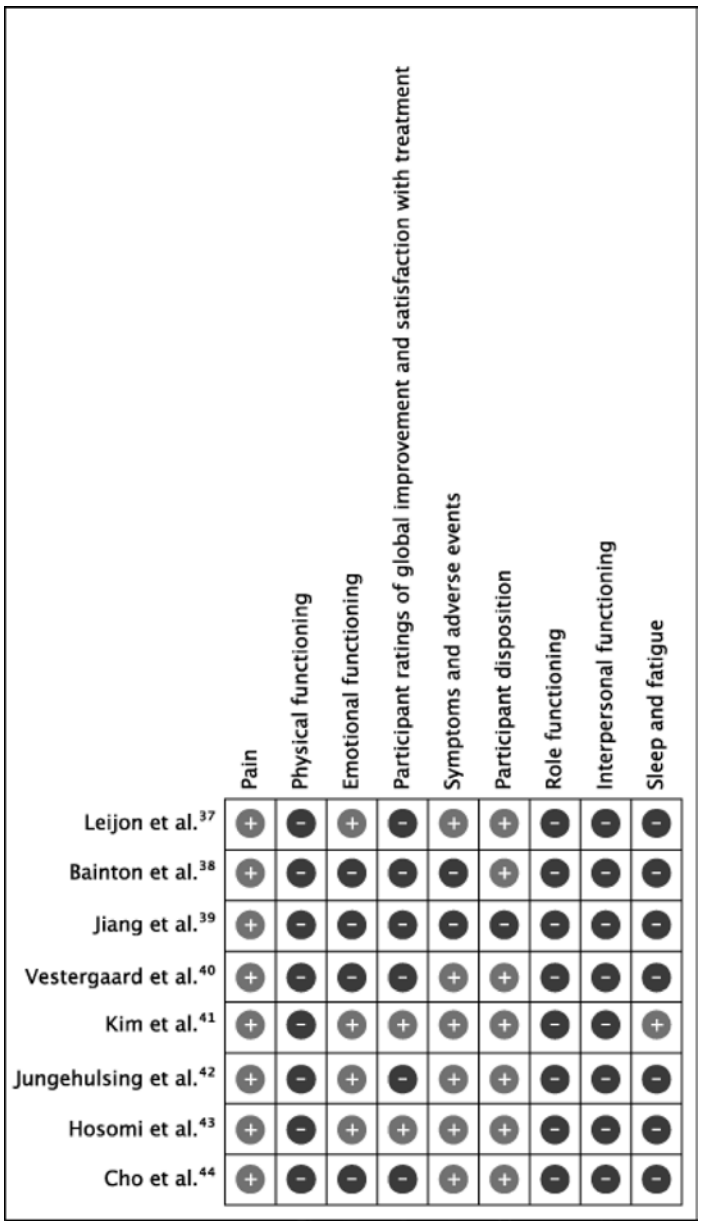


Table 1. Characteristics of eligible studies

Author	Country of Study	Study Design	Treatments	Frequency & Duration of Treatment	# Total CPSP Randomized	Age of CPSP participants	Sex of CPSP participants	Duration of CPSP	Participant Disposition / Notes
Leijon et al.[37]	Sweden	Crossover	1) Amitriptyline (75 mg, final dose) 2) Carbamazepine (800 mg, final dose) 3) Placebo	4 weeks (7 days washout)	15	Mean: 66 years Range: 53-74	Female: 3 Male: 12	Mean: 54 months Range: 11-154	1 participant discontinued intervention due to interaction with existing medication
Bainton et al.[38]	United Kingdom	Crossover	1) Naloxone (8 mg) 2) Placebo	One-time treatment (2-3 week washout)	20	Mean: 61.1 years Range: 45-74	Female: 13 Male: 7	Mean: 7.5 years Range: 1-20	3 participants withdrew due to adverse events
Jiang et al.[39]	China	Parallel	1) Electroacupuncture (30 minutes) 2) Carbamazepine (0.1 mg)	Frequency Electroacupuncture: once daily Carbamazepine: Thrice daily Duration 30 days	60	NR	Electroacupuncture Female: 10 Male: 20 Carbamazepine Female: 9 Male: 21	Electroacupuncture Mean: 3.6 months Control Mean: 3.8 months	NR
Vestergaard et al.[40]	Denmark	Crossover	1) Lamotrigine (200 mg, final dose) 2) Placebo	8 weeks (2 weeks washout)	30	Median: 59 years Range: 37-77	Female: 12 Male: 18	Median: 2 years Range: 0.3-12	3 participants withdrew due to adverse events 1 participant did not complete the first treatment period, but continued the study in the second treatment period 4 participants withdrew due to lack of efficacy 3 participants withdrew due to protocol violations
Kim et al.[41]	Asia Pacific region	Parallel	1) Pregabalin (600 mg/day, final maximum dose) 2) Placebo	12 weeks (4 weeks dose adjustment, 8 weeks maintenance)	220	Pregabalin Mean: 59.4 years SD: 9.8 Placebo Mean: 57.1 SD: 10.2	Pregabalin Female: 43 Male: 67 Placebo Female: 39 Male: 70	Pregabalin Mean: 2.2 years Range: 0.1-17.7 Placebo Mean: 2.5 Range: 0.2-14.1	1 participant did not receive intervention 9 participants withdrew due to reasons related to the study drug 27 participants withdrew due to reasons not related to the study drug

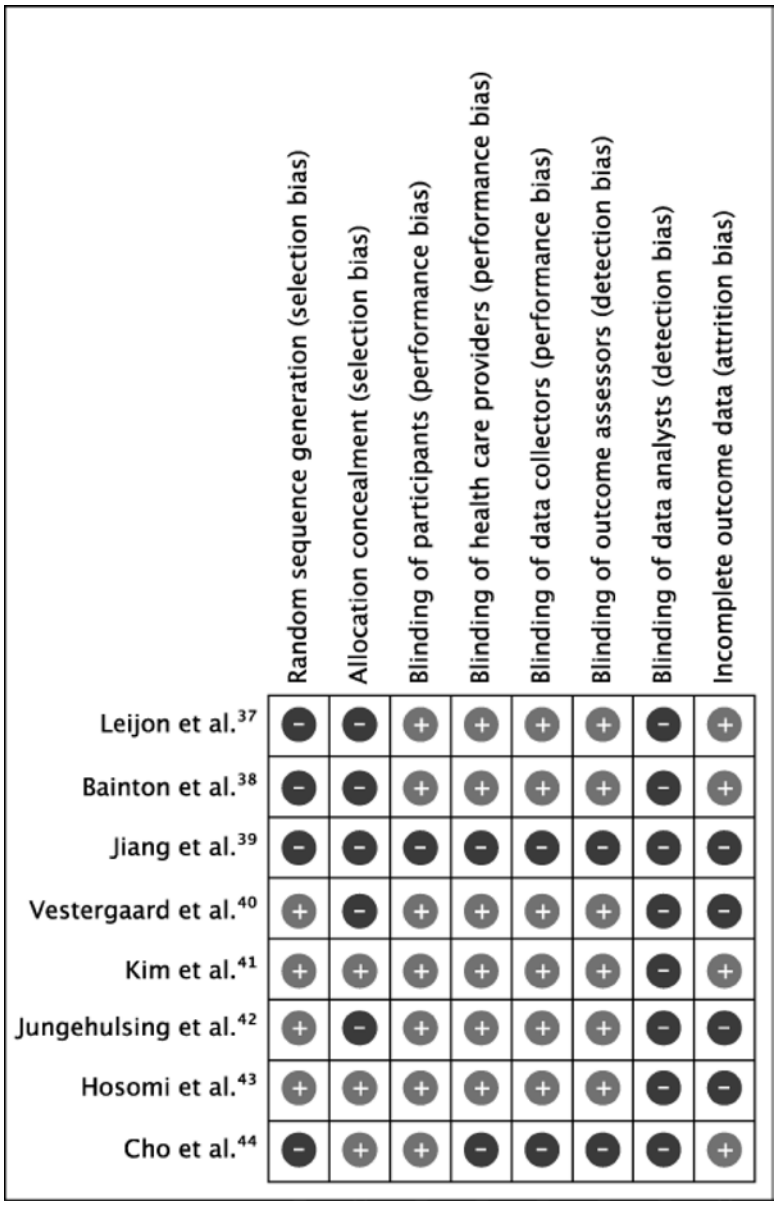
Jungehulsing et al.[42]	Germany	Crossover	1) Levetiracetam (3000 mg/day, maximum dose) 2) Placebo	8 weeks (2 weeks washout)	42	Median: 61.5 years Range: 40-76	Female: 16 Male: 26	Median: 4 years Range: 0.4-11	3 participants withdrew due to protocol violations 3 participants withdrew consent 3 participants withdrew due to adverse events
Hosomi et al.[43]	Japan	Crossover	1) Repetitive transcranial magnetic stimulation (5 Hz) 2) Sham stimulation	Once daily, 10 days (at least 17 days washout)	NR (See Notes)	NR	NR	NR	70 participants randomized (unclear how many with CPSP) 2 participants did not receive intervention (unclear how many with CPSP) 4 participants did not provide data (unclear how many with CPSP) 3 participants discontinued intervention (unclear how many with CPSP) 64 participants included in authors' intention-to-treat analysis set; 52 with CPSP
Cho et al.[44]	Republic of Korea	Parallel	1) Apipuncture (0.05 mL) 2) Saline Acupuncture	Twice weekly, 3 weeks	20	NR	NR	NR	1 participant withdrew due to adverse event 3 participants discharged/left hospital before follow-up

Figure 2. Reporting of IMMPACT-recommended outcome domains within included studies



(+) denotes presence of outcome domain; (-) denotes absence of outcome domain.

Figure 3. Risk of bias within included studies



(+) denotes low risk of bias; (-) denotes high risk of bias.

Figure 4A. Effects of anticonvulsants versus placebo on pain intensity (11-point scale, higher score is worse)

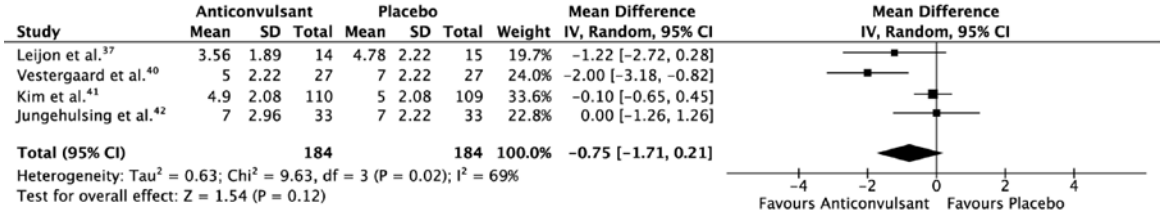


Figure 4B. Effects of anticonvulsants versus placebo on any adverse events

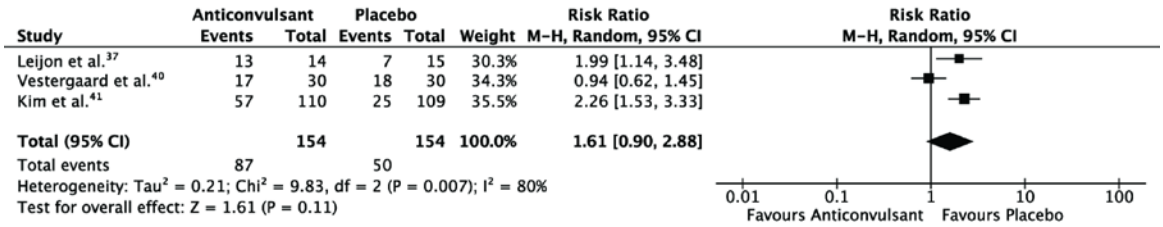


Table 2. GRADE Evidence Profile: Anticonvulsants vs. Placebo

Quality assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Anticonvulsants	Placebo	Relative (95% CI)	Absolute (95% CI)		
Pain intensity (follow up: range 4 to 12 weeks; assessed with: Visual Analogue Scale; 0 (no pain) to 10 (worst pain))												
4	randomised trials	serious [1]	serious [2]	not serious	serious [3]	undetected [4]	184	184	Not significant		⊕◯◯◯ VERY LOW	IMPORTANT
Any adverse event (follow up: range 4 to 12 weeks)												
3	randomised trials	serious [1]	serious [5]	not serious	serious [6]	undetected [4]	154	154	Not significant		⊕◯◯◯ VERY LOW	IMPORTANT
Depression (follow up: range 4 to 12 weeks; assessed with: Various instruments)												
3	randomised trials	serious [1]	not serious [7]	not serious	serious [3]	undetected [4]	145	145	No study found a significant reduction in depression symptoms		⊕⊕◯◯ LOW	IMPORTANT
Patient-reported global improvement (follow up: 12 weeks; assessed with: Patient Global Impression of Change; 1 (very much improved) to 7 (very much worse))												
1	randomised trial	serious [8]	not serious	not serious	serious [3]	undetected [4]	110	109	Not significant		⊕⊕◯◯ LOW	IMPORTANT
Sleep (follow up: 12 weeks; assessed with: Sleep Problems Index, Medical Outcomes Study Sleep Scale; 0 (no problems) to 100 (most severe problems))												
1	randomised trial	serious [8]	not serious	not serious	serious [3]	undetected [4]	110	109	Study found that pregabalin improved sleep versus placebo; difference between least-squares means: -4.2, 95% confidence interval: -8.4 to 0.0, p=0.049		⊕⊕◯◯ LOW	IMPORTANT

1. Serious due to selection bias (unclear and/or inadequate allocation concealment), detection bias (unclear blinding of data analysts), and attrition bias (incomplete outcome reporting)
2. Serious due to statistical heterogeneity (I^2 =69%; p=0.02)
3. Serious due to small sample size (<400 participants)
4. Insufficient number of studies to detect publication bias
5. Serious due to statistical heterogeneity (I^2 =80%; P=0.007)
6. Serious due to small number of events (<325)
7. Not serious due to all studies showing no significant treatment effect
8. Serious due to detection bias (unclear blinding of data analysts)

CHAPTER 4

At the time of writing this thesis, this chapter has been published in a peer-reviewed scientific journal, as follows:

Mulla SM, Buckley DN, Moulin DE, Couban R, Izhar Z, Agarwal A, Panju A, Wang L, Kallyth SM, Turan A, Montori VM, Sessler DI, Thabane L, Guyatt GH, Busse JW. Management of chronic neuropathic pain: a protocol for a multiple treatment comparison meta-analysis of randomized controlled trials. BMJ Open. 2014;4:e006112.

Management of chronic neuropathic pain: a protocol for a multiple treatment comparison meta-analysis of randomised controlled trials

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ABSTRACT

Introduction: Chronic neuropathic pain is associated with reduced health-related quality of life and substantial socioeconomic costs. Current research addressing management of chronic neuropathic pain is limited. No review has evaluated all interventional studies for chronic neuropathic pain, which limits attempts to make inferences regarding the relative effectiveness of treatments.

Methods and analysis: We will conduct a systematic review of all randomized controlled trials evaluating therapies for chronic neuropathic pain. We will identify eligible trials, in any language, by a systematic search of CINAHL, EMBASE, MEDLINE, AMED, HealthSTAR, DARE, PsychINFO, and the Cochrane Central Registry of Controlled Trials. Eligible trials will: (1) enrol patients presenting with chronic neuropathic pain, and (2) randomize patients to alternative interventions (pharmacological or non-pharmacological) or an intervention and a control arm. Pairs of reviewers will, independently and in duplicate, screen titles and abstracts of identified citations, review the full texts of potentially eligible trials, and extract information from eligible trials. We will use a modified Cochrane instrument to evaluate risk of bias of eligible studies, recommendations from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) to inform the outcomes we will

collect, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to evaluate our confidence in treatment effects. When possible, we will conduct: (1) in direct comparisons, a random-effects meta-analyses to establish the effect of reported therapies on patient-important outcomes; and (2) a multiple treatment comparison meta-analysis within a Bayesian framework to assess the relative effects of treatments. We will define *a priori* hypotheses to explain heterogeneity between studies, and conduct meta-regression and subgroup analyses consistent with current best practices.

Ethics and Dissemination: We do not require ethics approval for our proposed review. We will disseminate our findings through peer-reviewed publications and conference presentations.

Registration: PROSPERO (CRD42014009212).

STRENGTHS AND LIMITATIONS

- Our broad study eligibility criteria will allow us to generate more precise estimates of treatment effects, thus increasing generalizability of our results.

- We will use the GRADE approach to evaluate our confidence in treatment effects, and the IMMPACT guidelines to inform the outcomes we will collect. No existing review on the topic has done so.

- We will ensure interpretability by presenting both risk differences and measures of relative effect for all outcomes reported, and by presenting our findings with GRADE Evidence Profiles. No existing review on the topic has done so.

- Our results will be limited by possible shortcomings of the primary studies.

BACKGROUND

Chronic neuropathic pain is defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system."[1] It may be classified as central or peripheral, depending on the site of the lesion.[2] Among the causes of chronic neuropathic pain are metabolic disease (e.g. diabetes), infection (e.g. shingles), trauma (e.g. spinal cord injury), and autoimmune disease (e.g. multiple sclerosis).[3-5] The pain may be spontaneous or evoked in response to physical stimuli. The latter may manifest as increased sensitivity to pain (hyperalgesia) or as a painful response to a stimulus that would not normally be painful (allodynia).[4, 6]

Chronic neuropathic pain is common worldwide, affecting 7% to 10% of the general population.[7] It is associated with depression, anxiety, and sleep disturbances, and patients with chronic neuropathic pain experience lower health-related quality of life than the general population.[8-11]

Chronic neuropathic pain is associated with substantial economic burden. Tarride et al. estimated that managing a Canadian patient with chronic neuropathic pain over a three-month period costs an average of $2,567, of which 52% are direct costs, e.g. cost of physicians, diagnostic tests, and surgical procedures.[12] Others report that people suffering from chronic

neuropathic pain generate medical costs that are three times greater than those not living with pain.[11, 13] In the United States alone, almost $40 billion annually in health care, disability and related costs is attributed to chronic neuropathic pain.[4]

The underlying mechanisms of chronic neuropathic pain are poorly understood, which complicates management. Both non-pharmacological and pharmacological treatments are currently used. A limited number of systematic reviews focus on non-pharmacological options, including electrical nerve stimulation,[14] acupuncture,[15, 16] and cognitive behavioural therapy [17]. Most report pharmacological treatments for chronic neuropathic pain, including antidepressants,[18] anticonvulsants,[19] and opioid analgesics.[20]

Significant gaps remain though. For example, randomized controlled trials (RCTs) exploring treatment for chronic neuropathic pain often compare pharmacological treatments against placebo and seldom against each other. Consequently, there are few direct comparisons among treatments. A recent systematic review found that among 131 RCTs published between 1969 and 2007 and addressing painful diabetic neuropathy and postherpetic neuralgia, both common types of peripheral neuropathic pain, only 25 studies (19%) compared drugs directly against each other.[21]

No review to date has systematically evaluated all evidence for management of chronic neuropathic pain; existing reviews focus on select therapies [18, 20, 22-46] or specific syndromes.[47-57] Additionally, risk of bias assessment of studies included in existing reviews has been variable, and authors often depended on instruments that have been criticized for being overly simplistic (e.g. Jadad system) and/or assessed risk of bias on a per-study basis rather than overall for reported outcome.[58, 59] Furthermore, strategies to identify studies have been limited, as authors used few search terms, they did not search major literature databases, and/or they did not consider foreign language studies – an approach that would have excluded 12% of eligible trials in a systematic review of another chronic pain syndrome.[60] As well, none of the reviews employ the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the confidence in effect estimates (quality of evidence) for reported outcomes. And finally, none of the existing reviews facilitate interpretability, for instance, by presenting results in terms of minimally important differences (MID).

The limitations of previous works suggests the need for a new systematic review to be conducted using state-of-the-art methodology to inform evidence-based management of chronic neuropathic pain. We thus plan a systematic review and multiple treatment comparison meta-analysis of therapies for chronic neuropathic pain.

METHODS

Standardized Reporting

Our paper will conform to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews of RCTs.

Protocol Registration

Our protocol is registered on PROSPERO (registration number: CRD42014009212).

Search Strategy

We will identify relevant RCTs, in any language, by a systematic search of CINAHL, EMBASE, MEDLINE, AMED, HealthSTAR, DARE, PsychINFO, PapersFirst, ProceedingsFirst, and the Cochrane Central Registry of Controlled Trials, from the inception of each database. Our search will be refined for individual databases by a highly experienced medical librarian (RC) [Appendix 1 is a proposed search strategy for MEDLINE]. Reviewers will scan the bibliographies of all retrieved trials and other relevant publications, including reviews and meta-analyses, for additional relevant articles.

Eligibility criteria and their application to potentially eligible articles

Using standardized forms, reviewers trained in health research methodology will work in pairs to screen, independently and in duplicate, titles and abstracts of identified citations and acquire the full text publication of articles that both reviewers judge as potentially eligible. Using a standardized form, the same reviewer teams will independently apply eligibility criteria to the full text of potentially eligible trials. We will measure agreement between reviewers to assess the reliability of full-text review using the guidelines proposed by Landis and Koch.[61] Specifically, we will calculate Kappa values, and interpret them using the following thresholds: <0.20 as slight agreement, 0.21-0.40 as fair agreement, 0.41-0.60 as moderate agreement, 0.61-0.80 as substantial agreement, and >0.80 as almost perfect agreement. Eligible trials will: (1) enrol patients presenting with chronic neuropathic pain [Appendix 2 lists all syndromes we are studying], and (2) randomize patients to alternative interventions (pharmacological or non-pharmacological) or to an intervention and control arm.

Data Abstraction and Analysis

Before starting data abstraction, we will conduct calibration exercises to ensure consistency between reviewers. Teams of reviewers will extract data independently and in duplicate from each eligible study using standardized forms and a detailed instruction manual to inform tailoring of an online data abstraction program, DistillerSR (http://systematic-review.net/). We will

extract data regarding patient demographics, trial methodology, intervention details, and outcome data guided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).[62, 63] Specifically, we will collect outcome data across the following nine IMMPACT-recommended core outcome domains: (1) pain; (2) physical functioning; (3) emotional functioning; (4) participant ratings of improvement and satisfaction with treatment; (5) symptoms and adverse events; (6) participation disposition; (7) role functioning; (8) Interpersonal functioning; and (9) sleep and fatigue. We will collect data for all adverse outcomes as guided by Ioannidis and Lau.[64] We will resolve disagreements by discussion to achieve consensus.

Evaluating risk of bias in individual studies

Reviewers will assess risk of bias using a modified Cochrane risk of bias instrument that includes response options of "definitely or probably yes" – assigned a low risk of bias – or "definitely or probably no" – assigned a high risk of bias, an approach we have previously shown to be valid.[65] We will evaluate sequence generation, allocation sequence concealment; blinding of participants and study personnel; and, incomplete outcome data.[66] We will resolve any disagreements between reviewers by discussion. We will contact study authors if limitations in reporting lead to uncertainties in eligibility, risk of bias, or outcome.

Direct comparisons meta-analyses

In comparison to fixed effect models, random effect models are conservative in that they consider both within- and among-study variability. Recent methodological research has shown that while popular, the DerSimonian–Laird method [67] can produce narrow confidence intervals when the number of studies is small or when they are substantively heterogeneous.[68, 69] Therefore, to pool outcome data for trials that make direct comparisons between interventions and alternatives, we will use the likelihood profile approach.[70] We will pool cross-over trials with parallel design RCTs using methods outlined in the Cochrane handbook to derive effect estimates.[66] Specifically, we will perform a paired t-test for each crossover trial if any of the following are available: (1) the individual participant data; (2) the mean and standard deviation (SD) or standard error (SE) of the participant-specific differences and between the intervention and control measurement; (3) the mean difference (MD) and one of the following: (i) a t-statistic from a paired t-test; (ii) a P value from a paired t-test; (iii) a confidence interval from a paired analysis; or (4) a graph of measurements of the intervention arm and control arm from which we can extract individual data values, so long as the matched measurement for each individual can be identified.[66] If these data are not available, we will approximate paired analyses by calculating the MDs and the corresponding SEs for the paired analyses.[66] If the SE or SD of within-

participant differences are not available, we will impute the SD using the methods outlined in the Cochrane Handbook.[66]

Ensuring Interpretable Results

We will use a number of approaches to provide interpretable results from our meta-analyses. For studies that provide binary outcome measures, we will calculate relative risks (RRs) to inform relative effectiveness. To generate measures of absolute effect (risk differences), we will use estimates of baseline risk from the control arm of eligible RCTs.

When pooling across studies reporting continuous endpoints that use the same instrument, we will calculate the weighted mean difference (WMD), which maintains the original unit of measurement and represents the average difference between groups. Once the WMD has been calculated, we will contextualize this value by noting the corresponding MID – the smallest change in instrument score that patients perceive is important. We will prioritize use of anchor-based MIDs when available, and calculate distribution-based MIDs when they are not. We will also divide WMDs by their corresponding MID to obtain estimates in MID units. However, contextualizing the WMD through the MID can be misleading; clinicians may mistakenly interpret any effect in MID units smaller than 1 as suggesting no patient obtains an important benefit, and any effect estimate greater than 1 as suggesting that all patients benefit, which

is not accurate. Therefore, we will also calculate the proportion of patients who have benefited, i.e. demonstrated improvement greater than or equal to the MID in each trial, then aggregate the results across all studies.[71] Further, we will convert the proportion data to probabilities of experiencing benefit to calculate pooled RRs and numbers needed to treat (NNTs).

For trials that use different continuous outcome measures that address the same underlying construct, we will calculate the between-group difference in change scores (change from baseline) and divide this difference by the SD of the change. This calculation creates a measure of the effect (quantifying its magnitude in standard deviation units) called the standardized mean difference (SMD) that allows for comparison and pooling across trials.[66] However, the SMD is difficult to interpret and is vulnerable to the heterogeneity of patients that are enrolled: trials that enroll homogeneous study populations and thus have smaller standard deviations will generate a larger SMD than studies with more heterogeneous patient populations. To address this issue, we will calculate the effect estimates in MID units by dividing between-group difference in change scores by the MID. However, as with WMDs, contextualizing the SMD in MID units can be misleading; therefore, we will, for each trial, calculate the probability of experiencing a treatment effect greater than or equal to the MID in the control and intervention groups, then pool the results to calculate RRs and NNTs.[71]

Patients may be interested in the ability of a given intervention to provide more than an MID – to produce improvement that allows patients to feel much better (i.e. substantially greater than the MID), Thus, for our analyses, for studies that report percentage reduction in pain, we will also use thresholds of ≥20%, ≥30% and ≥50% reduction of pain from baseline to calculate the proportion of patients who have benefited in each trial, and derive RRs and risk differences.

Assessment of heterogeneity and subgroup analyses

We will conduct conventional meta-analyses (see above) for each paired comparison. For each of these comparisons, we will examine heterogeneity using both a chi-squared test and the I^2 statistic – the percentage of variability that is due to true differences between studies (heterogeneity) rather than sampling error (chance).[72, 73]

We have generated five *a priori* hypotheses to explain variability between studies: (1) subjective syndromes will show smaller treatment effects versus objectively diagnosed syndromes; (2) trials comparing treatment to placebo will show larger treatment effects than trials using active comparators; (3) trials that exclude patients who are receiving disability benefits and/or involved in litigation will show larger treatment effects than trials that include such patients; (4) chronic neuropathic pain syndromes defined by peripheral nervous

system lesions (e.g. diabetic neuropathy) will show larger effects that central nervous system lesions (e.g. chronic post-stroke pain); (5) trials with higher risk of bias will show larger treatment effects than trials with lower risk of bias; and, (6) trials with longer follow-up times will show smaller treatment effects than trials with shorter follow-up times. To inform our subgroup analyses based on risk of bias we will, if we detect variability within the individual risk of bias components, perform subgroup analyses on a component-by-component basis. We will perform meta-regression and subgroup analyses to explore these hypotheses, and interpret the results in the context of the GRADE system (see below).[74]

Confidence in the estimates of effect

We will use the GRADE approach to evaluate confidence in effect estimates for all reported outcomes.[75] GRADE has been adopted by over 70 organizations worldwide, and this approach facilitates transparent, rigorous and comprehensive assessment of evidence quality on a per outcome basis.[76-89] Our review of the management of chronic neuropathic pain will be the first to use the GRADE criteria to evaluate confidence in effect estimates. We will categorize the confidence in estimates (quality of evidence) as high, moderate, low, or very low. Using this approach, randomized trials begin as high quality evidence but may be rated down by one or more of four categories of limitations. We will use GRADE guidance to determine whether to rate down

confidence in the body of evidence for: (1) risk of bias;[87] (2) for imprecision; [81] for inconsistency;[83] and for publication bias.[84] For the risk of bias assessment, for any comparisons that suggest a statistically significant treatment effect, we will use recently developed approaches to address missing participant data for dichotomous outcomes and continuous outcomes.[90, 91] When plausible worst case scenarios reverse the treatment effect we will rate down for risk of bias. We will present the results of our meta-analyses in GRADE Evidence Profiles that will provide a succinct, easily digestible presentation of the risk of bias and magnitude of effects.[75]

Multiple treatment comparison meta-analyses

To assess relative effects of competing treatments, we will construct a random effects model within the Bayesian framework using Markov chain Monte Carlo methods.[92] We will use trace plots and calculate the Gelman-Rubin statistic to assess model convergence. We will model patient-important outcomes in every treatment group of every study, and specify the relations among the effect sizes across studies.[93] This method combines direct and indirect evidence for any given pair of treatments. We will use the resulting 95% credible intervals (CrIs) to assess the precision of treatment effects.[94] A key assumption behind multiple treatment comparison meta-analysis is that the analysed network is consistent or coherent, i.e. that direct and indirect evidence on the same comparisons do not disagree beyond chance. We will

identify and estimate incoherence by employing a mixed treatment comparisons incoherence model in the Bayesian framework.[95] For each comparison, we will note the direct estimates and associated CIs from the previous analysis and calculate the indirect estimate using a node splitting procedure as well as the network estimate. We will conduct a statistical test for incoherence between the direct and the indirect estimate.

We will have assessed confidence in estimates of effect from the direct comparisons in our pair-wise meta-analyses described previously. For rating confidence in the indirect comparisons, we will focus our assessments on first-order loops (that is, loops that are connected to the interventions of interest through only one other intervention; for example A versus C and B versus C to estimate effects of A versus B) with the lowest variances, and thus contribute the most to the estimates of effect. Within each loop, our confidence in the indirect comparison will be the lowest of the confidence ratings we have assigned to the contributing direct comparisons. For instance, if treatment A versus C warrants high confidence and B versus C warrants moderate confidence, we will judge the associated indirect comparison (A versus B) as warranting moderate confidence. We may rate down confidence in the indirect comparisons further if we have a strong suspicion that the transitivity assumption (i.e. the assumption that there are no effect modifiers - such as differences in patients, extent to which interventions have been optimally

administered, differences in the comparator, and differences in how the outcome has been measured - in the two direct comparisons that may bias the indirect estimate) has been violated.

Our overall judgement of confidence in the network estimate for any paired comparison will be the higher of the confidence rating amongst the contributing direct and indirect comparisons. However, we may rate down confidence in the network estimate if we find that the direct and indirect estimates are incoherent.

As a secondary analysis, we will rank the interventions using the SUCRA (surface under the cumulative ranking) method.[96] The SUCRA rankings may be misleading if there is only evidence warranting low confidence for most comparisons; if the evidence supporting the higher ranked interventions warrants lower confidence than the evidence supporting the lower ranked interventions; or if the magnitude of effect is very similar in higher versus lower ranked comparisons. We will consider these issues in interpreting the SUCRA rankings.

DISCUSSION

With the established high prevalence of chronic neuropathic pain worldwide, the associated high socioeconomic burden, and the paucity of evidence on the comparative effectiveness of treatment options, there is an urgent and critical need for a high-quality systematic review to inform evidence-based management of chronic neuropathic pain.

Our proposed review has several strengths in relation to existing reviews. First, we will include all non-pharmacological and pharmacological treatment options for all chronic neuropathic pain syndromes. It is plausible that individual pain syndromes, in general, respond similarly to similar interventions, and thus by pooling across individual syndromes, it may be possible to provide a more precise estimate of treatment effect. In addition, examining all therapies for all chronic neuropathic pain syndromes would provide comprehensive guidance for management of chronic neuropathic pain, which increases utility to health care providers, patients, and payers. Second, we will update the search to present date, explore a wider range of literature databases than existing reviews, and include eligible articles in all languages. Third, we will make all subjective decisions, including determining trial eligibility and collecting data, in teams of reviewers, independently and in duplicate, with assessments of the reproducibility of judgments. Fourth, we will focus on collecting patient-

important outcomes across IMMPACT-recommended core domains. Fifth, we will use the GRADE approach to evaluate our confidence in treatment effects. Sixth, we will ensure interpretability by presenting both risk differences and measures of relative effect for all outcomes reported, and by presenting our findings with GRADE Evidence Profiles. Seventh, we will generate a limited number of *a priori* subgroup hypotheses to explain heterogeneity of pooled estimates of treatment effect, and conduct meta-regression and subgroup analyses consistent with best current practices.

As with existing reviews, the results of our proposed systematic review will be limited by possible shortcomings of the primary studies, including presence of publication bias, high heterogeneity, and poor quality of reporting and methodological rigor. Another likely limitation, unique to multiple treatment comparison meta-analyses, will be the nature of available treatment comparisons to build robust networks for our analyses.

The findings of our review will help inform patients with chronic neuropathic pain about their therapeutic options, so that they can make more autonomous health management decisions. In addition, to help educate clinicians responsible for managing such patients, our review will facilitate updating clinical practice guidelines for the management of chronic neuropathic pain.

FOOTNOTES

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Contributors: All authors made substantial contributions to conception and design. SMM drafted the article, and DNB, DEM, RC, ZI, AA, AP, LW, SMK, AT, VM, DIS, LT, GHG, and JWB revised it critically for important intellectual content. All authors provided final approval of the version to be published.

Competing Interests: DEM and AP are chair and member, respectively, of the Canadian Pain Society Guideline Committee for management of chronic neuropathic pain. DEM has received research grant funding from Pfizer Canada, and has received honoraria for educational presentations from Jansenn-Ortho, Lilly, Purdue Pharma and Merck-Frosst. All other authors report no conflicts of interest.

Acronyms: CrIs: Credible intervals; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; IMMPACT: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; MD: Mean difference; MID: Minimally important difference; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs: Randomized controlled trials; RR:

Relative risk; SD: Standard deviation; SE: Standard error; SMD: Standardized mean difference; SUCRA: surface under the cumulative ranking; WMD: Weighted mean difference

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Appendix 1. Proposed search strategy for MEDLINE

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

[mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

Search Strategy:
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11 peripheral nervous system diseases/ or brachial plexus neuropathies/ or brachial plexus neuritis/ or complex regional pain syndromes/ or causalgia/ or reflex sympathetic dystrophy/ or diabetic neuropathies/ or giant axonal neuropathy/ or guillain-barre syndrome/ or mononeuropathies/ or femoral neuropathy/ or median neuropathy/ or peroneal neuropathies/ or radial neuropathy/ or sciatic neuropathy/ or sciatica/ or tibial neuropathy/ or tarsal tunnel syndrome/ or ulnar neuropathies/ or cubital tunnel syndrome/ or ulnar nerve compression syndromes/ or nerve compression syndromes/ or carpal tunnel syndrome/ or piriformis muscle syndrome/ or pudendal neuralgia/ or thoracic outlet syndrome/ or cervical rib syndrome/ or neuralgia/ or neuralgia, postherpetic/ or neuritis/ or polyneuropathies/ or alcoholic neuropathy/ or "hereditary sensory and motor neuropathy"/ or alstrom syndrome/ or charcot-marie-tooth disease/ or refsum disease/ or spastic paraplegia, hereditary/ or poems syndrome/ or polyradiculoneuropathy/ or polyradiculoneuropathy, chronic inflammatory demyelinating/ or polyradiculopathy/ or radiculopathy/ (92706)
2 exp central nervous system disease/ (1143738)
3 "autoimmune diseases of the nervous system"/ or myelitis, transverse/ or neuromyelitis optica/ or polyradiculoneuropathy/ or guillain-barre syndrome/ or "hereditary sensory and autonomic neuropathies"/ or polyradiculoneuropathy, chronic inflammatory demyelinating/ (10899)
4 Fabry Disease/ (2583)
5 Angiokeratoma/ (601)
6 Paraneoplastic Polyneuropathy/ (201)
7 Glossalgia/ (247)
8 Burning Mouth Syndrome/ (732)
9 Syringomyelia/ (3155)
10 Paroxysmal Hemicrania/ (75)
11 Trigeminal Autonomic Cephalalgias/ (105)
12 Phantom Limb/ (1528)
13 Thalamic Diseases/ (1103)
14 neuropath*.mp. (102493)
15 mononeuropath*.mp. (1492)

16 polyneuropath*.mp. (13247)
17 polyradiculoneuropath*.mp. (5027)
18 (Guillian adj Barre).mp. (87)
19 (Guillain adj Barre).mp. (7148)
20 (lewis adj sumner).mp. (49)
21 (charcot adj marie adj tooth).mp. (3790)
22 HMSN.mp. (432)
23 Peroneal muscular atrophy.mp. (165)
24 Guyon.ti,ab. (137)
25 Pronator teres.mp. (270)
26 (Struther$ adj ligament).mp. (18)
27 Wartenberg$.mp. (116)
28 Angiokeratoma.mp. (886)
29 (Anderson adj Fabry).mp. (208)
30 neuritis.mp. (13529)
31 neuronopath*.mp. (989)
32 myelinopath*.mp. (172)
33 distal axonopath*.mp. (229)
34 HIV-DSP.mp. (15)
35 Post-mastectomy pain.mp. (27)
36 Phantom limb.mp. (1828)
37 agnosia.mp. (2575)
38 plexopathy.mp. (723)
39 Radiculopathy.mp. (6164)
40 Glossodynia.mp. (136)
41 Stomatodynia.mp. (45)
42 (transverse adj myelitis).mp. (1338)
43 Fothergill*.mp. (75)
44 myelopath*.mp. (9661)
45 (Dejerine adj Roussy).mp. (37)
46 Syringomyelia.mp. (3784)
47 (Ramsay adj hunt).mp. (440)
48 (ramsey adj hunt).mp. (23)
49 sciatica.mp. (5358)
50 exp Multiple Sclerosis/ (44211)
51 exp Parkinsonian Disorders/ (58601)
52 parkinson.mp. (61412)
53 exp Stroke/ (85841)
54 (post adj stroke).mp. (3958)
55 thalamic*.mp. (24137)
56 exp Spinal Cord Injuries/ (37723)
57 cauda equina/ (2816)
58 cauda equina.mp. (4587)
59 exp Ophthalmoplegia/ (9669)

60 exp Herpes Zoster/ (9636)
61 postherpetic.mp. (1800)
62 Diabetic Neuropathies/ (12033)
63 small fiber.mp. (716)
64 exp HIV/ (84444)
65 hiv.mp. (275179)
66 or/1-65 (1625784)
67 neuropath*.mp. (102493)
68 neuralgi*.mp. (18296)
69 facial pain/ (5019)
70 phantom limb/ (1528)
71 phantom limb.mp. (1828)
72 CRPS.ti,ab. (1390)
73 CPSP.ti,ab. (157)
74 burning mouth syndrome/ (732)
75 dysesthe*.ti,ab. (1613)
76 (chronic adj2 pain).ti,ab. (31746)
77 pain measurement/ (60773)
78 or/67-77 (201452)
79 66 and 78 (119454)
80 Trigeminal Neuralgia/ (5540)
81 Facial Neuralgia/ (1121)
82 Facial Pain/ (5019)
83 Glossalgia/ (247)
84 Burning Mouth Syndrome/ (732)
85 Trigeminal Autonomic Cephalalgias/ (105)
86 neuralgia/ or neuralgia, postherpetic/ or piriformis muscle syndrome/ or pudendal neuralgia/ or sciatica/ (12818)
87 neuralgi*.mp. (18296)
88 Post-mastectomy pain.mp. (27)
89 postmastectomy pain syndrome.mp. (24)
90 PMPS.mp. (406)
91 Post-thoracotomy pain.mp. (234)
92 Phantom limb.mp. (1828)
93 agnosia.mp. (2575)
94 Glossodynia.mp. (136)
95 Stomatodynia.mp. (45)
96 (tic adj do?lo?re?ux?).mp. (300)
97 Prosopalgia.mp. (15)
98 meralgia paresthetica.mp. (277)
99 metatarsalgia.mp. (566)
100 (Ramsay adj hunt).mp. (440)
101 odontalgia.mp. (151)
102 sciatica.mp. (5358)

103 (Pain adj2 clinic).ti,ab. (1417)
104 (chronic adj2 pain).ti,ab. (31746)
105 (Neurogen* adj2 pain).ti,ab. (429)
106 low back pain/ (14091)
107 or/80-106 (77534)
108 79 or 107 (176257)
109 (dh or dt or pc or rh or rt or su or th).fs. (5395344)
110 exp Analgesia/ (31987)
111 exp Analgesics/ (433810)
112 analges*.mp. (140770)
113 treat*.mp. (4077132)
114 therap*.mp. (2410630)
115 intervention*.mp. (583724)
116 manag*.mp. (963377)
117 or/109-116 (8422296)
118 108 and 117 (104367)
119 randomized controlled trial.pt. (376906)
120 controlled clinical trial.pt. (88589)
121 randomized.ab. (297403)
122 placebo.ab. (155216)
123 drug therapy.fs. (1709609)
124 randomly.ab. (215113)
125 trial.ab. (308899)
126 groups.ab. (1367352)
127 or/119-126 (3364472)
128 exp animals/ not humans.sh. (3955572)
129 127 not 128 (2886355)
130 118 and 129 (36678)
131 limit 130 to "therapy (maximizes sensitivity)" (30615)
132 limit 131 to "review articles" (6311)
133 131 not 132 (24304)
134 Transcranial Magnetic Stimulation/ (6992)
135 rtms.mp. (2511)
136 magnetics/tu (807)
137 134 or 135 or 136 (8481)
138 pain.mp. (480976)
139 137 and 138 (542)
140 133 or 139 (24765)

Appendix 2. List of chronic neuropathic pain syndromes

- Central neuropathic pain
    - Parkinson disease-related pain
    - Compressive myelopathy from spinal stenosis
    - Post-traumatic spinal cord injury pain
    - Syringomyelia
    - HIV myelopathy
    - Multiple-sclerosis related pain
    - Post-ischemic myelopathy
    - Post-radiation myelopathy
    - Central post-stroke pain
        - Thalamic pain syndrome
        - Dejerine–Roussy syndrome
    - Transverse myelitis

- Peripheral neuropathic pain
    - Alcoholic neuropathy/polyneuropathy
    - Charcot-Marie-Tooth disease
        - Charcot-Marie-Tooth neuropathy
        - Hereditary motor and sensory neuropathy (HMSN)
        - Peroneal muscular atrophy (PMA)
    - Fabry disease (Fabry's disease, Anderson-Fabry disease, angiokeratoma corporis diffusum and alpha-galactosidase A deficiency)
    - Idiopathic sensory neuropathy
    - Nutritional deficiency-related neuropathies
        - Thiamine-deficiency neuropathy/beriberi neuropathy
    - Painful diabetic neuropathy
    - Axillary neuropathy
    - Complex regional pain syndrome
        - Reflex sympathetic dystrophy
        - Causalgia
    - Entrapment neuropathies (nerve compression syndromes, compression neuropathy)
        - Anterior interosseous syndrome
        - Carpal tunnel syndrome
        - Cubital tunnel syndrome
        - Guyon's canal syndrome
        - Posterior interosseous neuropathy
        - Pronator teres syndrome

    - Radial neuropathy
    - Struthers' ligament syndrome
    - Wartenberg's Syndrome
- Nerve compression or infiltration by tumour
- Post-mastectomy pain
- Post-thoracotomy pain
- Post-surgical/post-operative neuropathic pain
- Phantom limb pain
- Radiculopathy (cervical, thoracic or lumbosacral)
- Post-traumatic neuralgia
- Meralgia paresthetica (neuropathy of the lateral femoral cutaneous nerve)
- Obturator neruralgia
- Femoral neuralgia
- Sciatic neuralgia
- Morton's neuralgia (interdigital metatarsalgia)
- Piriformis syndrome(technically a variation on sciatic)
- Cauda equina syndrome
- Post mastectomy pain is sometimes referred to (in the IASP taxonomy) as post mastectomypain syndrome
- Post thoracotomy pain syndrome
- Internal mammary artery syndrome (post cardiac surgery Internal Mammary nerve neuralgia)
- Segmental or intercostal neuralgia
- Abdominal cutaneous nerve entrapment syndrome
- Neuralgias of the genitofemoral, ilioinguinal, iliohypogastric, or pudendal nerves
- Facial nerves - neuralgias associated with each and every nerve including the branches of the trigeminal (V1-2-3); 7th nerve (Ramsay Hunt syndrome); glossopharyngeal nerve
- Occipital neuralgias
- Painful opthalmoplegia;
- Odontalgia
- Thoracic outlet syndrome
- Acute and chronic inflammatory demyelinating polyradiculoneuropathy
    - Guillain–Barré syndrome
    - Lewis-Sumner syndrome
- Cancer-related neuropathy
    - Chemotherapy-induced peripheral neuropathy
    - Radiotherapy-induced peripheral neuropathy
- HIV-sensory neuropathy
    - HIV-associated distal sensory polyneuropathy (HIV-DSP)
- Postherpetic neuralgia

- Postradiation plexopathy
- Progressive inflammatory neuropathy
- Stomatodynia
  - Glossodynia
  - Burning mouth syndrome
- Toxic exposure-related neuropathies
- Trigeminal neuralgia (Tic douloureux)
  - Prosopalgia
  - Suicide disease
  - Fothergill's disease
- Vasculitic neuropathy
- Wartenberg's migratory sensory neuropathy

CHAPTER 5

FACTORS ASSOCIATED WITH DISABILITY BENEFITS CLAIM DURATION AMONG CANADIAN WORKERS: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Background: Disability insurance protects workers from total loss of income in case of a disabling injury or illness by providing wage-replacement benefits. We explored predictors of disability benefits claim duration to better inform early identification of claims at risk of prolonged recovery.

Methods: Using administrative data from SSQ Financial, a private Canadian disability insurer, we evaluated the association between nine variables and short-term disability (STD) and long-term disability (LTD) benefits duration with Cox proportional hazards regression analyses.

Results: We analyzed 70,776 STD and 22,205 LTD claims. For both STD and LTD claims, and across all disorders, older age, female gender, heavy job demands, presence of comorbidity, attending an independent medical evaluation, receipt of rehabilitation therapy, and longer time to claim approval were associated with longer claim duration. Higher pre-disability salary was associated with shorter STD claim duration. Quebec residency was associated with longer STD claim duration among workers with psychological disorders, but shorter STD claim duration among those with non-psychological illnesses. For LTD claims, however, residing in Quebec was associated with shorter claim duration, although the magnitude of the association differed across clinical conditions.

Interpretation: We identified several factors associated with STD and LTD claim duration, which may be helpful to identify claims at risk of prolonged recovery.

Our study has limitations, however, and well-designed prospective studies are needed to confirm our findings.

INTRODUCTION

The World Health Organization considers disability - including impairments, activity limitations, and participation restrictions - a complex phenomenon.[1] In 2012, according to the Canadian Survey on Disability, approximately 3.8 million Canadians (13.7% of the total population) reported a disability.[2] More females (14.9%) reported having a disability than males (12.5%), as did those in older versus younger age groups.[3] Almost 50% of adults reporting disabilities labeled their limitation as severe or a very severe,[4] and most reported living with multiple disabilities; for instance, almost 80% of individuals who reported pain-related disabilities also reported memory disabilities.[5]

Disabilities often create barriers for people to participate in the labour force, and the resulting financial implications can be substantial, especially for protracted absences from work.[6,7] Although workers' compensation plans are mandatory in Canada, and provide wage replacement benefits for most employees injured at work, they do not provide coverage for all workers or for non-work-related injuries or illnesses. Employees wishing to obtain coverage for disabling injuries or illnesses not covered by compensation boards can purchase disability benefits through private, for-profit, providers. These plans, which provide either short- or long-term benefits, provide partial wage-replacement benefits for workers who are deemed unable to work due to disabling injury or illness.

In Canada, short-term disability (STD) benefits plans typically provide benefits for 17 or 26 weeks. Long-term disability (LTD) coverage begins when STD benefits run out, with most policies providing coverage up to age 65, as long as claimants remain disabled from their own occupation for the initial two years of the claim, and disabled from any and all occupations for which they are qualified by training or experience after they have been on claim for 2 years, i.e. the change of definition period.

We have reported, in a study conducted in partnership with Sun Life Financial Canada, several administrative, clinical, and demographic factors associated with disability benefits claim duration among depressed workers.[8] It remains uncertain, however, whether these associations are consistent among other private insurers and other clinical conditions. This is important to establish, as improved understanding of factors associated with claim duration - especially those that are modifiable - may help insurers optimize case management policies and processes to facilitate faster recovery. Hence, we sought, using data from another private Canadian disability insurer – SSQ, Life Insurance Company Inc. – to identify factors associated with disability benefits duration among Canadian workers.

METHODS

Study design

Retrospective cohort study.

Standardized reporting

We followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement for reporting our study.[9]

Description of patients and eligibility criteria

We examined all claims SSQ approved for STD and/or LTD benefits from January 1, 2007 to March 31, 2014, which represented the most recent consecutive period for which SSQ collected data consistently and was available electronically.

In addition to offering standard benefit plans, SSQ offers "additional" STD and LTD plans, which may be paid simultaneously or subsequently to standard plans. The "additional" plans differ from the standard plans with respect to several factors, including financial, e.g. lower or greater portion of pre-disability salary paid, and administrative, e.g. shorter or longer duration to change in disability definition date. For our analyses, we only considered claimants who received one type of STD and/or LTD benefit plan. If a claimant

received both STD and LTD benefits, so long as each plan was only of one type, i.e. either standard or "additional," that claimant contributed twice to our analyses – once in the STD model, and once in the LTD model. We excluded claimants who received a General Expenses benefit plan, as these are a distinct type of plan for self-employed claimants, and those for whom the initial decision by the case manager was missing; together, these excluded claims represented <1% of all claimants.

Administrative variables

Guided by the results of our previous study[8] and content experts on our team, we selected, *a priori*, 10 variables we hypothesized may be associated with claim duration, and predicted the direction of anticipated effects (Table 1).

Claimants for whom SSQ manages both STD and LTD benefit plans do not undergo a separate approval process for the LTD claim; rather, this process is seamless, i.e. there is no delay between moving from STD to LTD benefits as long as claimants qualify. For such claimants, we used the duration of claim approval for the STD plan that SSQ recorded in its database, and imputed a value of 0 days to represent the duration of approval for the corresponding LTD plan. Additionally, we analyzed three previously untested variables: physical job demands, attendance at an independent medical evaluation (IME) arranged by SSQ, and receipt of rehabilitation service funded by SSQ. We considered

attending an IME and receiving rehabilitation as time-varying covariates to account for timing of initiation during the course of the benefits period.

Outcomes

Our primary outcomes were STD and LTD claim duration.

Data management and data cleaning

We screened all data to identify implausible values, inconsistencies, and missing data. If we identified implausible values and inconsistencies, we worked with SSQ to correct the data.

Statistical analysis

We report the mean and standard deviation (SD) of continuous variables that proved normally distributed, the median and interquartile range (first quartile [Q1] to third quartile [Q3]) for continuous variables that were not normally distributed, and the number of occurrences as percentages for categorical variables.

We tested for pairwise correlations between independent variables using a correlation matrix; if two variables were highly correlated, as indicated by a Pearson Correlation Coefficient (r) >0.80, we removed the variable that we deemed of lesser importance. Further, we tested for multicollinearity by

calculating the variance inflation factors (VIFs) associated with each independent variable in our models, and considered values ≥5 to indicate the presence of multicollinearity. If we detected multicollinearity, we removed the variable(s) that we deemed of lower importance.

We performed time-to-event analyses using Cox proportional hazards regression models to assess the association between the independent variables and duration of STD and LTD benefits. Our event was cessation of disability benefits. For STD claims that were active (receiving benefits) for 17 weeks (the most common STD benefit plan duration administered by SSQ) after claim approval, we used 118 days (17 weeks minus 1 day) as our censoring point. For LTD claims, we used the date of extraction as our censoring point. To avoid overfitting our models, we required ≥10 events per variable for our Cox regression model.[10] We excluded independent variables with <200 observations, unless we were able to collapse them with other related variables to exceed this threshold. To check that the proportional hazards assumption was met for each variable in our model, we calculated its interaction with time, while entering the remaining variables in the model without interactions. Statistical tests conducted when a data set is very large may, however, show statistical significance when the magnitude of effect is trivial. Therefore, when an interaction was significant, we calculated the hazard ratios (HRs) at different time-points, as follows: STD: 30 and 90 days; LTD: 180 days, 1 and 2.5 years; if

the HRs were very similar, i.e. did not differ by ≥0.20 across the time-points, we did not consider the proportional hazards assumption to be violated. We calculated HRs for our analyses, their associated 99% confidence intervals (CIs), and associated p-values. To minimize the likelihood of spurious findings, we considered an independent variable as statistically significant if it had a $p<0.01$ in each final adjusted model.

We conducted post-hoc analyses to explore if independent variables were consistently predictive of STD and LTD benefits duration across clusters of clinical conditions. We conducted our analyses for each of three subgroups of claimants, according to their pre-defined classification of illnesses: psychological disorders, musculoskeletal diseases, and other clinical conditions. Specifically, for each variable in our model, we calculated its interaction with clinical condition, while entering the remaining variables in the model without interactions. When an interaction was significant, we qualitatively compared the HRs across the subgroups for meaningful differences in effect sizes: if the HRs did not vary by ≥0.20 across the different models, we presented the effect sizes from the overall (pooled) model; if the HRs varied by ≥0.20, we presented the effects of the respective independent variable(s) separately.

We conducted all statistical analyses using SAS (version 9.3) and created plots using IBM SPSS Statistics (version 20.0).

Research ethics

The Hamilton Integrated Research Ethics Board approved our study.

RESULTS

Our study sample consisted of 70,776 STD and 22,205 LTD claims. We removed claim office from our final adjusted models, as it was highly correlated with claimants' province of residence (r=0.89 for STD model; r=0.93 for LTD model). Associated VIFs for the remaining independent variables were <2. Table 2 presents the baseline characteristics of all claimants eligible for our analysis.

Short-term disability

Of 70,776 STD claims, 57,158 (80.8%) were closed prior to 17 weeks, and 13,618 (19.2%) were censored. Figure 1 illustrates the benefits duration survival curve for STD claimants.

Our adjusted Cox regression analysis showed older age (HR [99% CI] = 0.87 [0.86 to 0.88], per decade), higher pre-disability salary (0.95 [0.92 to 0.99], per $1000 per week), female gender (0.88 [0.85 to 0.90]), heavy job demands (0.93 [0.90 to 0.96]), report of comorbidity (0.65 [0.63 to 0.67]), attending an IME (0.23 [0.20 to 0.27]), receipt of rehabilitation therapy (0.21 [0.18 to 0.25]), and longer time to claim approval (0.95 [0.95 to 0.96], per week) were associated with longer STD claim duration (Table 3). Claimants with psychological disorders who resided in Quebec were more likely (0.69 [0.63 to 0.74]) to have longer STD claims than those from other provinces; conversely, claimants with

non-psychological illnesses from Quebec were more likely to have shorter STD claims versus claimants from elsewhere in Canada: 1.15 [1.10 to 1.22] for musculoskeletal diseases; 1.08 [1.04 to 1.12] for other illnesses.

Long-term disability

Of 22,205 LTD claims, 17,474 (78.7%) were closed when we extracted our data, and 4,731 (21.3%) were censored. Figure 2 depicts the benefits duration survival curve for LTD claimants.

Our adjusted regression analysis showed older age (HR [99% CI] = 0.82 [0.80 to 0.83], per decade), female gender (0.94 [0.90 to 0.98]), heavy job demands (0.94 [0.89 to 0.99]), report of comorbidity (0.75 [0.72 to 0.79]), attending an IME (0.57 [0.53 to 0.61]), receipt of rehabilitation therapy (0.56 [0.52 to 0.59]), and longer time to claim approval (0.93 [0.92 to 0.94], per week) were associated with longer LTD claim duration (Table 4). Further, we found Quebec residency was associated with shorter LTD claim duration, although the magnitude of the effect varied according to claimants' clinical condition: 1.54 [1.38 to 1.71] for psychological disorders; 1.39 [1.28 to 1.51] for musculoskeletal diseases; 1.19 [1.10 to 1.28] for other illnesses.

Table 5 presents the comparison between our anticipated direction of effects and the observed results.

INTERPRETATION

Summary of main results

For both STD and LTD claims, older age, female gender, heavy job demands, presence of comorbidity, attending an IME, receipt of rehabilitation therapy, and longer time to claim approval were associated with longer claim duration. Higher pre-disability salary was associated with shorter STD claim duration. We found the association with residing in Quebec on STD benefits duration differed according to claimants' clinical conditions: it was associated with longer STD claim duration for psychological disorders, but shorter STD benefits duration for non-psychological illnesses. For LTD claims, however, residing in Quebec was associated with shorter claim duration, albeit to varying degrees according to clinical conditions.

Strengths and limitations of the study

Strengths of our study include *a priori* selection of independent variables for our regression models, including the anticipated direction of effects. Other strengths include no missing data, and correction of identifiable data errors and inconsistencies. The limitations of our study include our retrospective study design, which did not allow us to investigate certain variables in detail, e.g. reasons for arranging IMEs and rehabilitation, and a number of variables known to affect claim duration were unavailable, e.g., injury or illness severity. Second, our primary outcome, i.e. disability claim duration, underestimates

total disability duration, as benefits start date may not coincide with disability start date, especially among claimants who qualify for LTD benefits, but have to wait (elimination period) before receiving payments. Further, claim closure is a surrogate for patient-important outcomes, such as functional recovery and sustained return to work.[8]

Findings in context of previous evidence

Our findings are consistent with a previous study, in which data from another private Canadian insurer suggested, among claimants with depression, older age, female gender (STD claims only), higher salary, and co-morbidity were associated with longer claim duration.[8] In that study, prolonged time to claim approval was only associated with longer LTD claim duration. Here, however, we found longer claim approval duration is associated with longer STD and LTD claim duration. Given the seamless transition between STD and LTD claims at SSQ, our findings suggest LTD claims are shorter when SSQ manages the preceding STD claim as well. Other approaches to minimizing time to claim approval may be a promising target for reducing claim duration. Previously, residing in Quebec (versus Ontario) was associated with longer STD claim duration, but shorter LTD claim duration.[8] We report a similar association among claimants with psychological disorders who resided in Quebec versus elsewhere in Canada. Among claimants with non-psychological conditions, however, Quebec residency was associated with shorter STD and LTD benefits

duration. Systematic differences in claim management policies and processes in Quebec may explain variation in claim duration. For instance, dissimilarities in legal systems between Quebec (civil law) and other provinces (common law) may impact the extent to which disability insurance contracts could be prematurely terminated. Further, more Quebec residents than those living in the rest of Canada belong to labour unions, e.g. teachers, government officials, and hospital staff. Union members' disability insurance contracts (LTD only) include elimination periods, sometimes as long as 2 years, which could influence claim duration.

Our results are consistent with previous evidence suggesting high job demands are associated with delayed recovery.[11-16] Contrary to our hypotheses, however, we found claimants who attended an IME or received rehabilitation service are more likely to experience prolonged claim duration. We were unable to adjust for injury or illness severity, and it is possible these interventions are largely directed towards claimants who are sicker or more seriously injured, and would for that reason experience longer claim duration. Our findings are, however, consistent with observations in patients with whiplash injury, in which receipt of early rehabilitation has not been associated with faster recovery even after adjusting for severity of injury.[17-19] Further, previous evidence indicates individuals with external financial incentives, e.g. disability benefits, may experience poorer health outcomes than those who do not.[20-23] Moreover, many

randomized controlled trials examining the effectiveness of therapies do not enrol patients receiving compensation.[24] Data from such trials cannot be confidently extrapolated to patients who are receiving compensation. Our results highlight an urgent need for trials exploring the effect of rehabilitation among patients receiving disability benefits.

Conclusion and future directions

We found several predictors of STD and LTD benefits duration, including two previously untested variables – attendance at an IME and receipt of rehabilitation. All factors but claimants' province of residence were consistently predictive of benefits duration, irrespective of clinical condition. Our results provide a direction for randomized trials that address modifiable determinants of sustained return to work, including time to claim approval. Such studies would usher in an era of evidence-based disability management.

FOOTNOTES

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Table 1. Description of variables

Variable	Description	Anticipated direction of claim closure (for both STD and LTD claims unless otherwise stated)
Age	Claimant's age at the beginning of disability	Older age: (-)
Gender	Claimant's gender	Female: (-)
Salary	Claimant's pre-disability gross income	Higher salary: (-)
Job demands	Physical demands of claimant's job	Heavy: (-) Light: (-)
Province	Claimant's province of residence	Quebec: (-) for STD, (+) for LTD
Comorbidity	If claimant has a secondary illness recorded in their claim file	Comorbidity present: (-)
Office	If a claim was received at Quebec or National office	Quebec: (-) for STD, (+) for LTD
Attendance at IME	If claimant has attended an IME	Attendance at IME: (+)
Receipt of rehabilitation	If claimant has received rehabilitation funded by SSQ Financial or not	Receipt of rehabilitation: (+)
Duration of claim approval	Duration from disability claim registration date to disability claim contractual approval date	Longer duration of claim approval: (-)

STD: short term disability; LTD: long term disability; IME: Independent Medical Evaluation; (-) associated with slower claim closure; (+) associated with faster claim closure.

Table 2. Baseline characteristics

Variable	STD, n(%)	LTD, n(%)
Total claimants	70776	22205
Age: Median (Q1 to Q3) years	46 (36 to 53)	48 (40 to 54)
Gender		
Male	31068 (43.9%)	10052 (45.3%)
Female	39708 (56.1%)	12153 (54.7%)
Monthly salary: Median (Q1 to Q3)	$3695.5 ($2915.5 to $4546.5)	$3521.8 ($2799.8 to $4546.5)
Job demands		
Sedentary	22586 (31.9%)	8104 (36.5%)
Light	30217 (42.7%)	8604 (38.8%)
Heavy	17973 (25.4%)	5497 (24.8%)
Province		
Quebec	59117 (83.5%)	16700 (75.2%)
Other	11659 (16.5%)	5505 (24.8%)
Illness		
Psychological disorder	15294 (21.6%)	7325 (33.0%)
Musculoskeletal disease	22124 (31.3%)	7165 (32.3%)
Other	33358 (47.1%)	7715 (34.7%)
Comorbidity		
Yes	10381 (14.7%)	6447 (29.0%)
No	60395 (85.3%)	15758 (71.0%)

Receipt of SSQ Financial-facilitated IME*		
Yes	1341 (1.9%)	2275 (10.3%)
No	64435 (98.1%)	19930 (89.8%)
Receipt of SSQ Financial-funded rehabilitation*		
Yes	1098 (1.6%)	2552 (11.5%)
No	69678 (98.5%)	19653 (88.5%)
Time to claim approval: Median (Q1 to Q3) weeks	1.0 (0.9 to 1.9)	2.4 (1.1 to 5.6)

STD: Short-term disability; LTD: Long-term disability; Q1: first quartile; Q3: third quartile; IME: Independent medical evaluation.

*At some point during benefits period.

Table 3. Determining factors predictive of time to short-term disability benefits duration based multivariable Cox regression analysis

Factor	HR	99% CI for HR		P-value
		Lower	Upper	
Age (per 10 years)	0.87	0.86	0.88	<0.0001
Salary (per $1000 per week)	0.95	0.92	0.99	0.0003
Gender				
Female vs. Male (reference group)	0.88	0.85	0.90	<0.0001
Job demands				
Heavy vs. Sedentary (reference group)	0.93	0.90	0.96	<0.0001
Light vs. Sedentary (reference group)	0.99	0.97	1.02	0.4963
Province				
Quebec vs. Other (reference group) by Psychological disorder	0.69	0.63	0.74	<0.0001
Quebec vs. Other (reference group) by Musculoskeletal disease	1.15	1.10	1.22	0.0084
Quebec vs. Other (reference group) by Other illness	1.08	1.04	1.12	0.0003
Comorbidity				
Yes vs. No (reference group)	0.65	0.63	0.67	<0.0001
Receipt of IME				
Yes vs. No (reference group)	0.23	0.20	0.27	<0.0001
Receipt of rehabilitation				
Yes vs. No (reference group)	0.21	0.18	0.25	<0.0001
Duration of claim approval (weeks)	0.95	0.95	0.96	<0.0001

HR: Hazard ratio; CI: Confidence interval; IME: Independent medical evaluation.
HR >1 is associated with faster claim closure; HR <1 is associated with slower claim closure.

Table 4. Determining factors predictive of time to long-term disability benefits duration based on multivariable Cox regression analysis

Factor	HR	99% CI for HR		P-value
		Lower	Upper	
Age (per 10 years)	0.82	0.80	0.83	<0.0001
Salary (per $1000 per week)	1.02	0.97	1.08	0.3525
Gender				
Female vs. Male (reference group)	0.94	0.90	0.98	0.0001
Job demands				
Heavy vs. Sedentary (reference group)	0.94	0.89	0.99	0.0022
Light vs. Sedentary (reference group)	1.02	0.98	1.07	0.1912
Province				
Quebec vs. Other (reference group) by Psychological disorder	1.54	1.38	1.71	<0.0001
Quebec vs. Other (reference group) by Musculoskeletal disease	1.39	1.28	1.51	0.0003
Quebec vs. Other (reference group) by Other illness	1.19	1.10	1.28	<0.0001
Comorbidity				
Yes vs. No (reference group)	0.75	0.72	0.79	<0.0001
Receipt of IME				
Yes vs. No (reference group)	0.57	0.53	0.61	<0.0001
Receipt of rehabilitation				
Yes vs. No (reference group)	0.55	0.52	0.59	<0.0001
Duration of claim approval (weeks)	0.93	0.92	0.94	<0.0001

HR: Hazard ratio; CI: Confidence interval; IME: Independent medical evaluation.
HR >1 is associated with faster claim closure; HR <1 is associated with slower claim closure.

Figure 1. Kaplan Meier (survival) curve of short-term disability duration

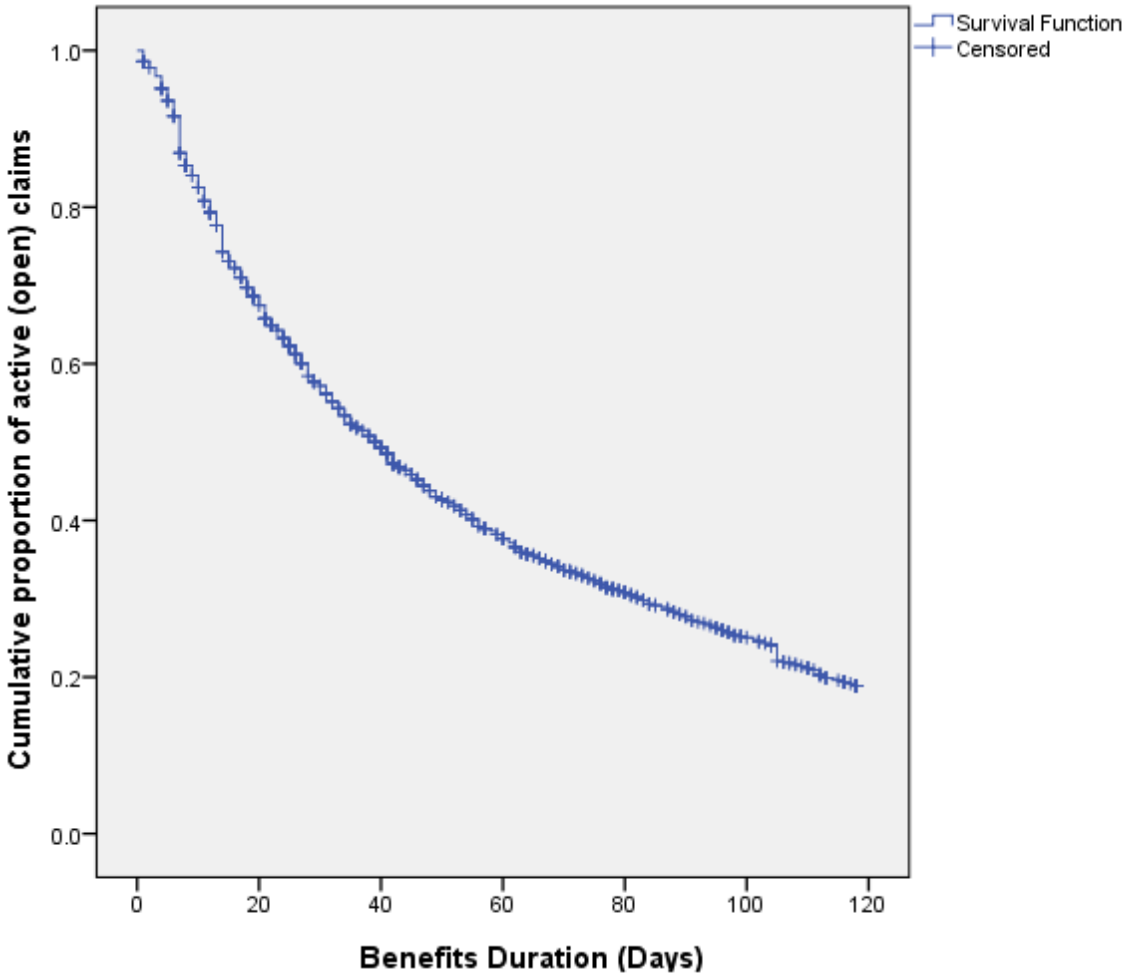

Figure 2. Kaplan Meier (survival) curve of long-term disability duration

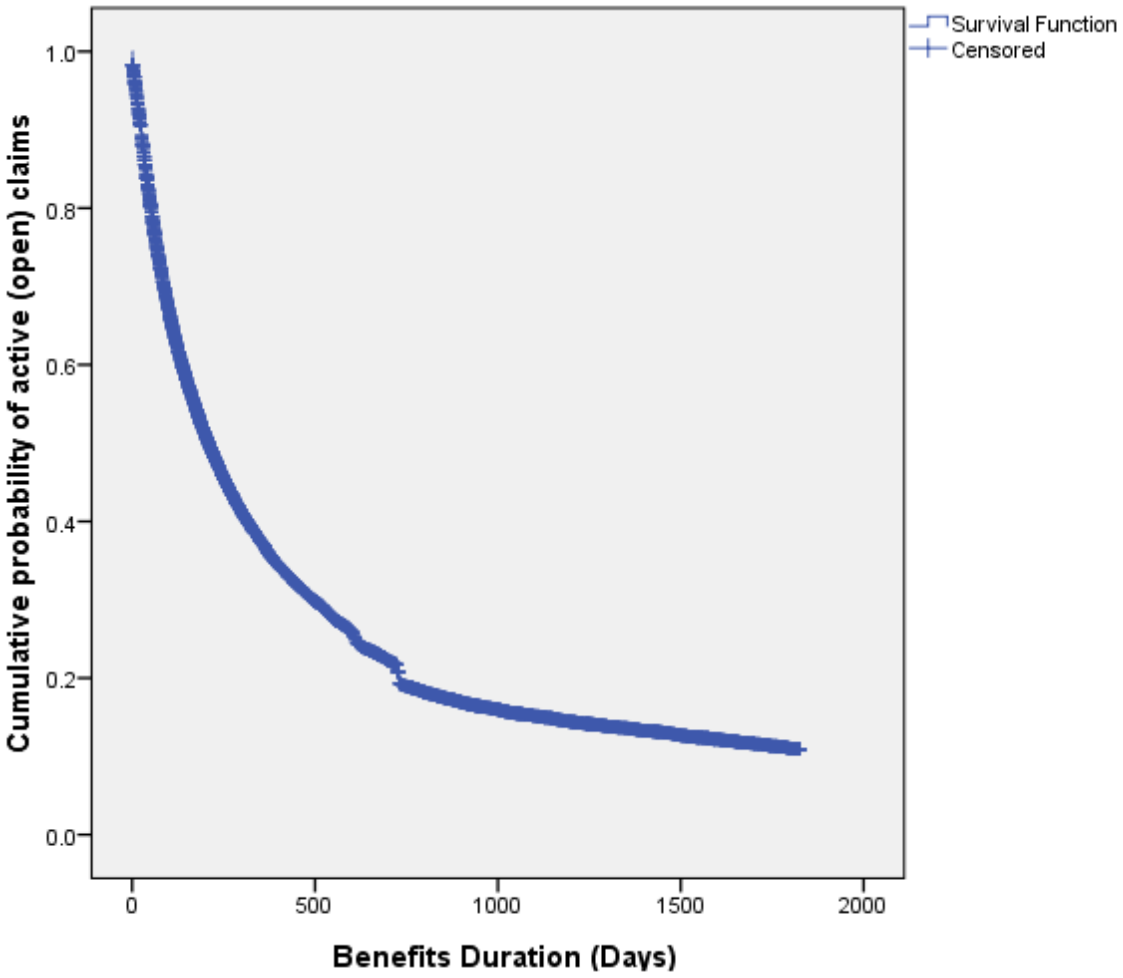

Table 5. Comparison between predictors associated with time to claim closure for short-term disability versus long-term disability claims

Predictor	STD	LTD	Anticipated direction
Older age	-	-	-
Higher salary	-	NS	-
Female (versus males)	-	-	-
Heavy job demands (versus sedentary)	-	-	-
Light job demands (versus sedentary)	NS	NS	-
Quebec residency (versus else)	- for claimants with psychological disorders, + for claimants with musculoskeltal diseases and other illnesss	+	- for STD, + for LTD
Presence of comorbidity (versus no comorbidity)	-	-	-
Attending an IME (versus not attending an IME)	-	-	+
Receipt of rehabilitation (versus no receipt of rehabiltiation)	-	-	+
Longer time to claim approval	-	-	-

STD: Short-term disability; LTD: Long-term disability; IME: Independent medical evaluation; +: Associated with faster claim closure; -: Associated with slower claim closure; NS: Not significant

CHAPTER 6

CONCLUSION

Overview

This thesis focused on issues related to optimizing the management of patients with CNCP, as well as of individuals in receipt of disability benefits. In this chapter, I discuss key findings, limitations, and future directions arising from the work that contributed to this thesis.

Management of patients with CNCP

This thesis begins, in **Chapter 1**, with a methodological study to evaluate the extent to which clinical trials of opioids for CNCP evaluated and reporting treatment effects across nine patient-important outcomes domains recommended by IMMPACT. Among 156 randomized controlled trials, reporting of IMMPACT domains was highly variable, ranging from 7% for interpersonal functioning to 99% for pain. Several factors, including date of publication, corresponding author location, and journal impact factor, were associated, to varying degrees, with reporting the IMMPACT domains. Most domains showed an increased rate of reporting over time, although many remained unreported by over half of all trials. We found publication of IMMPACT recommendations was not associated with increased reporting of IMMPACT-recommended core

outcome domains, which is contrary to previous beliefs. As we only evaluated trials testing the effectiveness and safety of opioids, however, our findings may not be generalizable to other chronic pain clinical trials.

At the end of this study, an important issue with which our group grappled was balancing the merits and challenges of evaluating and reporting treatment effects across multiple outcome domains. On one hand, it is conceivable that, without consistent and more complete reporting of patient-important outcomes, trialists will be unable to fully convey the effects of a given treatment for CNCP. This is especially true when considering evidence suggesting the relationship between pain relief and improvements in other outcome domains is inconsistent. Conversely, however, measurement of nine outcomes, as IMMPACT recommends, may threaten the feasibility and validity of trials by increasing participant burden, which could result in more missing data or errors. Exploration of why chronic pain clinical trialists do not include comprehensive measurement of all domains and improved guidance from IMMPACT to address potential feasibility concerns warrant attention.

To further explore optimal management options for patients with CNCP, in **Chapter 3**, we conducted a systematic review of randomized controlled trials of all therapies (pharmacological and non-pharmacological) for CPSP. Eight eligible English-language RCTs, which enrolled 459 patients, tested four

anticonvulsants, an antidepressant, an opioid antagonist, repetitive transcranial magnetic stimulation, and two modes of acupuncture. Results suggested that all therapies had little to no effect on pain and other patient-important outcomes. We noticed similar trends in the extent to which these trials reported treatment effects across the nine IMMPACT domains as the opioid trials from the previous chapter. Our certainty, according to the GRADE approach, in the treatment estimates ranged from very low to low, which limited the clinical utility of our results. To deal with this issue, we suggest investigators should conduct large, multi-center, randomized trials to assess patient-important outcomes.

Following the results of our study, we compared the findings of our systematic review with clinical practice guidelines by three major professional groups – the IASP NeuPSIG, EFNS, and CPS – and found their recommendations were inconsistent with the available evidence. We noticed, however, these recommendations were based on the success of treatments, such as anticonvulsants, in patients with other chronic neuropathic pain conditions. This assumes that treatment responses are consistent across chronic neuropathic pain conditions. There is some empirical evidence to support this hypothesis, but we are exploring it further in an ongoing systematic review of all therapies for all chronic neuropathic pain conditions. The protocol for this larger review, which includes a network meta-analysis, comprises **Chapter 4** of

this thesis. In developing this protocol, we convened an international team of 15 experts, which includes researchers and clinicians from across North America. To help facilitate maximum uptake of the results of this study, we developed a comprehensive knowledge translation program. For instance, we connected with researchers from the Mayo Clinic to plan use the findings of our study to develop and test decision aids that will educate patients with chronic neuropathic pain about their therapeutic options. Further, we collaborated with the CPS to update their guidelines for managing chronic neuropathic pain based on the findings of this review; in doing so, we involved patient representatives, specifically from ACTION Ontario and the Canadian Pain Coalition. Last, we engaged several healthcare policy makers in the public and private sectors, including a large Canadian private disability insurer, all of whom committed to using this review's findings to inform reimbursement policies for therapies for chronic neuropathic pain.

Management of individuals in receipt of disability benefits

With the support of the same disability insurer as above, I also completed a retrospective cohort study, which constituted **Chapter 5** of my thesis, to explore predictors of disability benefits claim duration. Our study sample consisted of 70,776 STD and 22,205 LTD individuals who received wage-replacement benefits as a result of a disabling injury or illness. Across STD and LTD claims, irrespective of claimants' primary clinical condition, older age,

female gender, heavy job demands, presence of comorbidity, receipt of IME and rehabilitation therapy, and longer duration of claim approval were associated with longer benefits duration. Higher pre-disability salary was associated with shorter STD benefits duration. Only the effects of claimants' province of residence on claim duration differed by their clinical condition.

Our results are, however, limited by several issues, including absence of important variables, e.g., injury or illness severity, and a sub-optimal primary outcome. Still, our findings are largely consistent with a previous study, in which members of our group analyzed the data from another large Canadian private insurer. In particular, longer time to claim approval is consistently associated with longer claim duration. Testing whether claim approval duration is definitively associated with benefits duration would be of particular interest to private insurers. If these companies can set up criteria to expedite all claims (especially LTD) in a timely manner, this may reduce overall claim duration and improve claim resolution rates by allowing claimants to focus on recovery early on versus focusing on "proving" how sick they are to qualify for benefits. We could test this hypothesis via a cluster randomized trial, in which we would randomize groups or "clusters," for instance regional insurance offices, to follow either a rapid adjudication process or adjudication-as-usual for their LTD claim applications. We would then measure the difference in average LTD claim duration and claim resolution rates between the two clusters to estimate

whether the rapid adjudication process is successful, i.e. we observe a significant reduction in LTD claim duration and improved LTD claim resolution rates after implementing the rapid process versus following the usual process. Such a trial would provide evidence to either support or refute a change in case management policies and processes at insurance companies.

Our study also found a significant association between two previously untested factors – receipt of IME and rehabilitation – and benefits duration. Specifically, claimants who received an IME or rehabilitation, at some point during their claims, were at increased risk of prolonged claim durations. Members of our research group have found that patients presenting for IMEs commonly exaggerate their symptoms, especially those with external incentives, e.g. disability benefits. Thus, it remains plausible that claimants asked to undergo IMEs systematically represent more complex cases to manage. Additionally, sub-optimal rehabilitation could impede recovery, but without knowing the details of the services that the claimants in our study received, we can only speculate of the results we generated. These findings, however, warrant further investigation. In all, researchers should design and conduct large, prospective, ideally randomized, trials that will allow for optimal exploration of modifiable factors associated with sustained return to work.