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

BY

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McMaster University

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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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Dissertation supervisor
Thank you Dr. Jason Busse for his outstanding mentorship and unqualified commitment to my personal and professional growth. His unique combination of superb intellect and unrelenting light-hearted witticism led to academic discussions that were equal parts enlightening and entertaining. I am proud to consider Jason a lifelong colleague and a dear friend, and will forever be indebted to him for all he continues to do for me.

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Thank you to all the study co-authors with whom I the privilege to work.

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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. Prevalence rates are higher among women, and older individuals. CNCP has a marked negative impact on quality of life and physical functioning.

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{14} Individuals with CPSP commonly experience sensory abnormalities, including increased tactile and thermal sensitivities, which significantly impact their quality of life.\textsuperscript{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. 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. In 2014, full-time employees in Canada took an average of 7.4 sick days, while United Kingdom workers lost 131 million days due to sickness absence in 2013. 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. 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, and a greater number of older workers taking sick leave versus younger workers, 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. 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.
References


CHAPTER 2

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


Wolters Kluwer Health, Lippincott Williams & Wilkins ©
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 ($\Phi$) 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 $\geq$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

**Funding:** This is a sub-study of a systematic review funded by the Canadian Institutes of Health Research (CIHR). SMM is supported by an Ontario Graduate Scholarship. SE is supported by a MITACS Elevate Fellowship Award and a SickKids Restraccump Postdoctoral Fellowship Award. GHG is supported by a CIHR Health Researcher of the Year Prize.

**Acknowledgements:** The authors thank Samantha Craigie for her assistance with coordinating this research study, and Rachel Couban for developing the search strategy and conducting the literature searches.

**Competing interests:** All authors report no conflicts of interest.
REFERENCES


Table 1. Study characteristics

<table>
<thead>
<tr>
<th>Country of Study (n=156), n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>66 (42.3%)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>18 (11.5%)</td>
</tr>
<tr>
<td>Canada</td>
<td>16 (10.3%)</td>
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<tr>
<td>France</td>
<td>8 (5.1%)</td>
</tr>
<tr>
<td>Germany</td>
<td>8 (5.1%)</td>
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<tr>
<td>Sweden</td>
<td>8 (5.1%)</td>
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<tr>
<td>Australia</td>
<td>5 (3.2%)</td>
</tr>
<tr>
<td>Italy</td>
<td>4 (2.5%)</td>
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<tr>
<td>Belgium</td>
<td>3 (1.9%)</td>
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<tr>
<td>Norway</td>
<td>3 (1.9%)</td>
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<tr>
<td>Denmark</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Other¹</td>
<td>15 (9.5%)</td>
</tr>
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| Impact factor (n=147),² median (IQR) | 2.8 (2.2 to 5.6) |

<table>
<thead>
<tr>
<th>Funding (n=156), n (%)</th>
<th></th>
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<tbody>
<tr>
<td>Not reported</td>
<td>67 (42.9%)</td>
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<tr>
<td>Exclusively industry-funded</td>
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<td>Funded by non-Industry</td>
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<tr>
<td>Not funded</td>
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<table>
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<tr>
<td>Not registered</td>
<td>142 (91.0%)</td>
</tr>
<tr>
<td>Registered</td>
<td>14 (9.0%)</td>
</tr>
</tbody>
</table>

| 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%) |

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

²7 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

<table>
<thead>
<tr>
<th>Outcome Domain</th>
<th>Number of trials (n=156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>154 (98.7%)</td>
</tr>
<tr>
<td>Symptoms and adverse events</td>
<td>146 (93.6%)</td>
</tr>
<tr>
<td>Participant disposition</td>
<td>118 (75.6%)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>71 (45.5%)</td>
</tr>
<tr>
<td>Participant ratings of improvement and satisfaction with treatment</td>
<td>67 (42.9%)</td>
</tr>
<tr>
<td>Sleep and fatigue</td>
<td>49 (31.0%)</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>44 (28.2%)</td>
</tr>
<tr>
<td>Role functioning</td>
<td>29 (18.6%)</td>
</tr>
<tr>
<td>Interpersonal functioning</td>
<td>11 (7.1%)</td>
</tr>
</tbody>
</table>
Table 3. Source of information for IMMPACT-recommended core outcome domains

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical condition(s)</th>
<th>Generic name of opioid</th>
<th>Dosage of opioid treatment</th>
<th>Frequency of opioid treatment</th>
<th>Duration of opioid treatment</th>
<th>Route of administration of opioid treatment</th>
<th>Top 3* most commonly reported adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arkinstall W, Sandler A, Goughnour B, Babul N, Harsanyi Z, Darke AC.</td>
<td>Various chronic non-cancer pain conditions</td>
<td>Codeine (controlled-release)</td>
<td>100, 150 or 200 mg</td>
<td>2 times daily</td>
<td>7 days</td>
<td>Oral</td>
<td>Nausea, headache, constipation/dizziness</td>
</tr>
<tr>
<td>Arner S, Meyerson BA.</td>
<td>Various chronic non-cancer pain conditions</td>
<td>Morphine</td>
<td>15 mg for patients with neuropathic pain; 10-20 mg for idiopathic pain</td>
<td>1 time treatment</td>
<td>1 time treatment</td>
<td>Intravenous</td>
<td>Not reported</td>
</tr>
<tr>
<td>Attal N, Guirand F, Brasseur L, Gaude V, Chauvin M, Bouhassira D.</td>
<td>Central neuropathic pain (due to stroke or spinal cord injury)</td>
<td>Morphine</td>
<td>Initial dose was set according to maximum tolerable dose during run-in period</td>
<td>1 time treatment</td>
<td>1 time treatment</td>
<td>Intravenous</td>
<td>Somnolence, vomiting, nausea</td>
</tr>
<tr>
<td>Babul N, Novack R, Chipman H, Roth SH, Gana T, Albert K.</td>
<td>Chronic pain due to osteoarthritis (knee)</td>
<td>Tramadol (extended-release)</td>
<td>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)</td>
<td>1 time daily</td>
<td>12 weeks</td>
<td>Oral</td>
<td>Dizziness, nausea, constipation</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Type</td>
<td>Pain Type</td>
<td>Drug Combination</td>
<td>Dose Description</td>
<td>Duration</td>
<td>Route</td>
<td>Adverse Effects</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Beaulieu AD, Peloso PM, Harauzi B, Bensen W, Thomson G, Wade J, Quigley P, Eisenhoffer J, Harsanyi Z, Darke AC</td>
<td>Once-daily, controlled-release tramadol and sustained-release diclofenac</td>
<td>Chronic pain due to osteoarthritis</td>
<td>Tramadol (controlled-release)</td>
<td>200 mg (initial dose) titrated weekly to 200, 300, 400 mg (maximum dose)</td>
<td>6 weeks</td>
<td>Oral</td>
<td>Dizziness, nausea, constipation</td>
</tr>
<tr>
<td>Bennett RM, Kamin M, Karim R, Rosenthal N</td>
<td>Combination of tramadol / acetaminophen</td>
<td>Fibromyalgia</td>
<td>37.5 mg</td>
<td>1 to 2 tablets (4 time daily) for a maximum of 8 tablets</td>
<td>91 days</td>
<td>Oral</td>
<td>Nausea, dizziness, somnolence</td>
</tr>
<tr>
<td>Blasi G, Manca S, Manganelli S, Marcolongo R</td>
<td>Combination of tramadol / acetaminophen</td>
<td>Fibromyalgia</td>
<td>100 mg per 2 mL</td>
<td>1 time treatment</td>
<td>1 time treatment</td>
<td>Oral</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Blondell RD, Ashrafioun L, Dambra CM, Foschio EM, Zielinski AL, Saucedo DM</td>
<td>Combination of buprenorphine / naloxone</td>
<td>Various chronic non-cancer pain conditions</td>
<td>2 mg</td>
<td>3-4 times daily, up to 16 mg daily</td>
<td>6 months</td>
<td>Oral</td>
<td>None reported</td>
</tr>
<tr>
<td>Bohme K</td>
<td>Buprenorphine</td>
<td>Various chronic non-cancer pain conditions</td>
<td>Study 1: 0.8-1.2 mg, Study 2: 35, 52.5, or 70 μg (per hour), Study 3: 35 μg (per hour)</td>
<td>Study 1: 2 patch applications, Study 2: 5 patch applications, Study 3: 3 patch applications</td>
<td>Study 1: 6 days, Study 2: 15 days, Study 3: 9 days</td>
<td>Transdermal patch</td>
<td>Nausea, vomiting, dizziness</td>
</tr>
<tr>
<td>Borges J, Zavaleta C</td>
<td>Combination of hydroxyzine / acetaminophen / propoxyphene / caffeine</td>
<td>Tension headache</td>
<td>Propoxyphene: 30 mg</td>
<td>1-2 tablets (initial dose) increased to 1 tablet every 4-6 hours daily</td>
<td>4 weeks</td>
<td>Oral</td>
<td>Drowsiness, dizziness</td>
</tr>
<tr>
<td>Authors</td>
<td>Title</td>
<td>Pain Type</td>
<td>Dosing</td>
<td>Duration</td>
<td>Route</td>
<td>Adverse Effects</td>
<td></td>
</tr>
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<td>---------------------------------</td>
<td>-----------------------------------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Boureau F, Boccard E</td>
<td>Placebo-controlled study of the analgesic efficacy of a combination of paracetamol and codeine in rheumatoid arthritis. Acta Ther 1991;17(2):123-136.</td>
<td>Chronic pain due to rheumatoid arthritis</td>
<td>Combination of paracetamol / codeine Codeine: 30 mg 1 tablet, 3 times daily 7 days Oral</td>
<td>7 days</td>
<td>Constipation, nausea, vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boureau F, Delecroceillerie G, Orvain J.</td>
<td>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.</td>
<td>Chronic non-inflammatory rheumatic pain</td>
<td>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</td>
<td>Nausea, constipation, drowsiness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breivik H, Ljosaa KM, Stengaard-Pedersen K, Persson J, Aro H, Villumsen J, Tvinneose D</td>
<td>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.</td>
<td>Chronic pain due to osteoarthritis</td>
<td>Buprenorphine 5 µg per hour (initial dose) titrated to 10 or 20 µg per hour, as needed 1 patch lasting 7 days 6 month Transdermal patch</td>
<td>Nausea, constipation, vomiting, constipation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>Chronic pain due to osteoarthritis</td>
<td>Oxycodone (controlled-release) or combination of oxycodone (immediate-release) / acetaminophen</td>
<td>Oxycodone (controlled-release): 10 mg; combination treatment: 5-325 mg</td>
<td>Oxycodone (controlled-release): 2 times daily; combination treatment: 4 times daily</td>
<td>60 days</td>
<td>Oral</td>
<td>Nausea, vomiting, drowsiness</td>
</tr>
<tr>
<td>Dallas T, Lin R, Wu W, Wolskee P.</td>
<td>Epidural morphine and methylprednisolone for low-back pain. Anesthesiology 1987;67(3):408.</td>
<td>Chronic low back pain</td>
<td>Morphine</td>
<td>8 mg per 8 mL of saline</td>
<td>1 time treatment</td>
<td>1 time treatment</td>
<td>Injection (epidural)</td>
</tr>
<tr>
<td>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.</td>
<td>Postherpetic neuralgia</td>
<td>Morphine</td>
<td>0.075 mg/kg</td>
<td>1 time treatment</td>
<td>1 time treatment</td>
<td>Intravenous</td>
<td>Fatigue, dizziness, feeling of unreality</td>
</tr>
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</tr>
<tr>
<td>Eidenach 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.</td>
<td>Chronic pain due to pancreatitis</td>
<td>ADL 10-0101 (κ-opioid receptor agonist)</td>
<td>10 µg</td>
<td>2 infusions sessions</td>
<td>60 minutes</td>
<td>Intravenous</td>
<td>No side effects reported</td>
</tr>
<tr>
<td>Emkey R, Rosenblatt 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.</td>
<td>Chronic pain due to osteoarthritis (knee or hip)</td>
<td>Combination of tramadol / acetaminophen</td>
<td>37.5 mg</td>
<td>1 tablet (every 3 days) to a maximum of 8 tablets daily</td>
<td>91 days</td>
<td>Oral</td>
<td>Nausea, constipation, dizziness</td>
</tr>
<tr>
<td>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.</td>
<td>Various chronic pain conditions</td>
<td>Tapentadol (immediate-release) or oxycodone (immediate-release)</td>
<td></td>
<td></td>
<td>28 days</td>
<td>Oral</td>
<td>Nausea, constipation, vomiting</td>
</tr>
<tr>
<td>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</td>
<td>Fentanyl</td>
<td>Initial dose was set according to the dose that provided stable pain control during the run-in phase</td>
<td>Up to 8 times daily</td>
<td>12 weeks</td>
<td>Oral</td>
<td>Nausea, dizziness, somnolence</td>
<td></td>
</tr>
<tr>
<td>Opioid-Tolerant Patients with Noncancer-Related Chronic Pain. Pain Med 2010;11(9):1313-1327.</td>
<td>Chronic pain due to osteoarthritis (knee)</td>
<td>Tramadol</td>
<td>50 mg (initial dose) titrated in 50 mg increments to a target dose of 200 mg daily</td>
<td>1 tablet, 4 times daily</td>
<td>91 days</td>
<td>Oral</td>
<td>Nausea, constipation, dizziness</td>
</tr>
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<tr>
<td>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.</td>
<td>Chronic neuropathic pain</td>
<td>Dihydrocodeine</td>
<td>30 mg (initial dose) titrated weekly to 60, 120, 240 mg (maximum dose)</td>
<td>1 time daily</td>
<td>6 weeks</td>
<td>Oral</td>
<td>Tiredness, sleeplessness, sickness</td>
</tr>
<tr>
<td>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.</td>
<td>Painful diabetic neuropathy</td>
<td>Combination of tramadol / acetaminophen</td>
<td>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)</td>
<td>Up to 1-2 tablets 4 times daily</td>
<td>66 days</td>
<td>Oral</td>
<td>Nausea</td>
</tr>
<tr>
<td>Friedman AP, DiSerio FJ.</td>
<td>Tension headache</td>
<td>Combination of acetaminophen / codeine</td>
<td>Not reported</td>
<td>2 capsules at 5 designated times over a 4 hour period</td>
<td>4 hours</td>
<td>Oral</td>
<td>Dizziness, nausea, abdominal discomfort</td>
</tr>
<tr>
<td>--------------------------</td>
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</tr>
<tr>
<td>Friedman AP. Assessment of Fiorinal with Codeine in the treatment of tension headache. Clin Ther 1986;8(6):703-721.</td>
<td>Tension headache</td>
<td>Codeine-alone or combination of butalbital / caffeine / aspirin / codeine</td>
<td>Codeine: 30 mg (alone or combination treatment)</td>
<td>4 capsules (2 per headache within 24 hrs of each other) daily</td>
<td>4 hours</td>
<td>Oral</td>
<td>Not reported</td>
</tr>
<tr>
<td>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.</td>
<td>Chronic pain due to osteoarthritis (knee or hip)</td>
<td>Tramadol (extended-release)</td>
<td>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).</td>
<td>1 time daily</td>
<td>12 weeks</td>
<td>Oral</td>
<td>Constipation, dizziness, nausea</td>
</tr>
<tr>
<td>Gazi NB, Sakata RK, Issy AM. Intra-articular morphine versus bupivacaine for knee motion among patients with osteoarthritis:</td>
<td>Chronic pain due to osteoarthritis (knee)</td>
<td>Morphine</td>
<td>1 mg</td>
<td>1 time treatment</td>
<td>1 time treatment</td>
<td>Intra-articular injection</td>
<td>Not reported</td>
</tr>
<tr>
<td>Study</td>
<td>Condition</td>
<td>Treatment</td>
<td>Dose</td>
<td>Duration</td>
<td>Route</td>
<td>Adverse Effects</td>
<td></td>
</tr>
<tr>
<td>-------</td>
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<td></td>
</tr>
<tr>
<td>Gilron I, Bailey JM, Tu D, Holden RR, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med 2005;352(13):1324-1334.</td>
<td>Painful diabetic neuropathy or postherpetic neuralgia</td>
<td>Morphine (sustained-release) or combination of morphine (sustained-release) / gabapentin</td>
<td>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)</td>
<td>2 times daily</td>
<td>5 weeks</td>
<td>Oral</td>
<td>Constipation, sedation, dry mouth</td>
</tr>
<tr>
<td>Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. Neurology 2003;60(6):927-934.</td>
<td>Painful diabetic neuropathy</td>
<td>Oxycodone (controlled-release)</td>
<td>10 mg daily (initial dose) daily to 60 mg (daily)</td>
<td>1 tablet (2 times daily) to 6 tablets (2 times daily)</td>
<td>6 weeks</td>
<td>Oral</td>
<td>Constipation, nausea, somnolence</td>
</tr>
<tr>
<td>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.</td>
<td>Chronic pain due to rheumatoid arthritis</td>
<td>Combination of paracetamol / codeine</td>
<td>Codeine: 30 mg</td>
<td>1 tablet, 3 times daily</td>
<td>7 days</td>
<td>Oral</td>
<td>Abdominal pain, malaise, pruritus</td>
</tr>
<tr>
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<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Group GPR. Migraine treated with an antihistamine-analgesic combination. Practitioner 1973;211(263):357-361.</td>
<td>Migraine</td>
<td>Combination of buclizine / paracetamol / codeine or combination of paracetamol / codeine</td>
<td>Codeine: 8 mg (both combinations)</td>
<td>2 tablets per attack (initial dose), 0.5 tablet at 30 minute intervals, up to a maximum of 4 tablets per attack</td>
<td>24 hours</td>
<td>Oral</td>
<td>Nausea, dizziness</td>
</tr>
<tr>
<td>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</td>
<td>Migraine</td>
<td>Combination of dextropropoxyphene / acetylsalicylic acid / antipyrine</td>
<td>Dextropropoxyphene: 100 mg</td>
<td>7 times</td>
<td>Variable (treatment given for 7 migraine attacks)</td>
<td>Oral</td>
<td>Nausea, vomiting, dizziness</td>
</tr>
<tr>
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<td>---</td>
<td>---</td>
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<td>---</td>
</tr>
<tr>
<td>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.</td>
<td>Chronic low back pain</td>
<td>Oxymorphone (extended-release)</td>
<td>Initial dose was 2 times daily dose of opioid that was approximatively 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.</td>
<td>2 times daily</td>
<td>12 weeks</td>
<td>Oral</td>
<td>Constipation, somnolence, nausea</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Study Design</td>
<td>Condition</td>
<td>Treatment</td>
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<td>Hartrick C, Van Hove I, Stegmann J-U, Oh C, Upmalis D.</td>
<td>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.</td>
<td>Clin Ther</td>
<td>2009</td>
<td>31(2):260-271.</td>
<td>Chronic pain due to joint disease</td>
<td>Tapentadol (immediate-release), or oxycodone (immediate-release)</td>
<td>Tapentadol (immediate-release): 50 mg or 75 mg; oxycodone (immediate-release): 10 mg</td>
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<th>Study</th>
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<th>Route</th>
<th>Side Effects</th>
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<th>Duration</th>
<th>Route</th>
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<tbody>
<tr>
<td>Jorum E, Warncke T, Stubhaug A.</td>
<td>Cold allodynia and hyperalgesia in neuropathic pain: the effect of N-methyl-D-aspartate (NMDA) receptor antagonist ketamine-a double-blind, cross-over</td>
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<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Treatment</th>
<th>Dosage</th>
<th>Route</th>
<th>Adverse Effects</th>
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<tr>
<td>Kagan G, Masheter HC.</td>
<td>Tension headache</td>
<td>Combination of paracetamol / codeine / doxylamine succinate / caffeine</td>
<td>Codeine: 10 mg</td>
<td>Oral</td>
<td>2 tablets (initial dose) increased to 6 tablets every 4-6 hours daily</td>
</tr>
<tr>
<td>Katz N, Hale M, Morris D, Stauffer J.</td>
<td>Chronic pain due to osteoarthritis</td>
<td>Combination of morphine / naltrexone (extended-release)</td>
<td>20 mg daily, titrated to a maximum of 160 mg daily</td>
<td>Oral</td>
<td>1 to 2 times daily</td>
</tr>
<tr>
<td>Katz N, Rauck R, Ahdieh H, Ma T, Gerritsen van der Hoop R, Kerwin R, Podolsky G.</td>
<td>Chronic low back pain</td>
<td>Oxymorphone (extended-release)</td>
<td>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</td>
<td>Oral</td>
<td>2 times daily</td>
</tr>
<tr>
<td>Kean WF, Bouchard S, Roderich Gossen E.</td>
<td>Chronic pain due to osteoarthritis (knee)</td>
<td>Tramadol</td>
<td>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</td>
<td>Oral</td>
<td>1 time daily</td>
</tr>
<tr>
<td>Keskinbora K, Aydınıl I.</td>
<td>Chronic ischemic lower extremity pain</td>
<td>Combination of bupivacaine / morphine</td>
<td>Morphine: 10 mg in 20 mL saline</td>
<td>Intravenous</td>
<td>1 time treatment</td>
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</table>

**Note:** The table provides a summary of treatments for various conditions, including their dosages, routes, and potential adverse effects. The dosages and treatment regimens are specified for each condition to illustrate the variability and complexity in pain management strategies.
<table>
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<tbody>
<tr>
<td>Chronic lumbar root pain</td>
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<tr>
<td>Chronic pain due to osteoarthritis (knee or hip)</td>
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<tr>
<td>2 times daily</td>
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<table>
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<tbody>
<tr>
<td>Chronic pain due to osteoarthritis of the hip</td>
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<tr>
<td>3 times daily</td>
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<tbody>
<tr>
<td>Painful diabetic neuropathy</td>
</tr>
<tr>
<td>Tramadol: 37.5mg</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>Study</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Kupers RC, Konings H, Adriaensen H, Gybels JM.</td>
</tr>
<tr>
<td>Laiq H, Khan MN, Iqbal Mj, Khan S.</td>
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<tr>
<td>Landau CJ, Carr WD, Razzetti AJ, Sessler NE, Munera C, Ripa SR.</td>
</tr>
<tr>
<td>Lane PL, McLellan BA, Bagooley CJ.</td>
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<td>Langford R, McKenna F, Ratcliffe S, Vojtassak J, Richarz U.</td>
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<td>Larkin GL, Prescott JE.</td>
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<tr>
<td>Leung A, Wallace M, 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.</td>
</tr>
<tr>
<td>List T, Tegelberg A, Haraldson T, Isacsson G. Intra-articular morphine as analgesic in temporomandibular joint arthralgia/osteoarthritis. Pain 2001;94(3):275-282.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>Malone 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,</td>
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<tr>
<td>Reference</td>
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<tr>
<td>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.</td>
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<tr>
<td>Matsumoto AK, Babul N, Adleie H. Oxymorphine 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.</td>
</tr>
<tr>
<td>Max MB, Byas-Smith MG, Gracely RH, Bennett GJ. Intravenous infusion of the NMDA antagonist, ketamine, in chronic posttraumatic pain with alldynia: a double-blind comparison to alfentanil and placebo. Clin Neuropharmacol 1995;18(4):360-368.</td>
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<td>Author(s)</td>
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<tr>
<td>Messick RT.</td>
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<td>Morley JS, Bridson J, Nash TP, Miles JB, White S, Makin NW.</td>
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<td>Morrison J, Ling F, Forman E, Bates G, Blake P, Vecchio T, Linden C, O'Connell M.</td>
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<tr>
<td>Munera C, Drehoibl M, Sestler N, Landau C. A randomized, placebo-controlled, double-blind, parallel-group, 5-week study of buprenorphine transdermal system in adults with osteoarthritis.</td>
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<td>Norrbrink C, Lundeberg T.</td>
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<td>Nuki G, Downie WW, Dick WC, Whaley K, Spooner JB, Darby-Dowman MA, Buchanan WW.</td>
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<td>Author(s)</td>
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<tr>
<td>Peloso PM, Bellamy N, Benson W, Thomson GT, Harsanyi Z, Babul N, Darke AC.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>Procacci P, Buzzelli G, Grazzini M, Monafò V. A controlled trial of a new analgesic (Z424) in experimental and pathological pain in comparison with codeine and aminopyrine. Curr Pain</td>
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<tr>
<td>--------------------------------------</td>
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<tr>
<td>Coxarthrosis pain</td>
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<tr>
<td>Postherpetic neuralgia</td>
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<td>Chronic pain due to post-laminectomy syndrome</td>
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<td>Chronic pain due to osteoarthritis</td>
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<td>Chronic pain due to osteoarthritis</td>
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<tr>
<td>Study</td>
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<tr>
<td>Roth SH. Efficacy and safety of tramadol HCl in breakthrough musculoskeletal pain attributed to osteoarthritis. J Rheumatol 1998;25(7):1358-1363.</td>
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<td>Rowbotham MC, Reisner-Keller LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia. Neurology 1991;41(7):1024-1028.</td>
</tr>
<tr>
<td>Ruoff GE. Slowing the initial titration rate of tramadol improves tolerability. Pharmacotherapy 1999;19(1):88-93.</td>
</tr>
<tr>
<td>Russell IL, 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.</td>
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<td>Schnitzer TJ, Kamin M, Olson WH.</td>
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<td>Scopa J, Jorgensen PB, Foster JB.</td>
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<td>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.</td>
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<tr>
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<td>Chronic pain due to osteoarthritis flare pain (knee or hip)</td>
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<tr>
<td>Polyneuropathy</td>
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<tr>
<td>Migraine</td>
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<tr>
<td>Fibromyalgia</td>
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<tr>
<td>Condition</td>
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</tr>
<tr>
<td>Various chronic pain conditions</td>
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<tr>
<td>Trigeminal neuralgia</td>
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<td>Chronic pathological pain</td>
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<td>Migraine</td>
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<td>Chronic osteoarthritis. S Afr Med J 1987;Suppl:1, 4-6.</td>
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<tr>
<td>A combination of ibuprofen and codeine phosphate provides superior analgesia to ibuprofen alone in osteoarthritis.</td>
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<td>The association between negative affect and opioid analgesia in patients with discogenic low back pain.</td>
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<td>Morphine is effective for treatment of chronic pain.</td>
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<td>Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy.</td>
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<tr>
<td>Oxytrex minimizes physical dependence while providing effective analgesia: a randomized controlled trial in low back pain.</td>
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<td>Morphine versus mexiletine for treatment of postamputation pain: a randomized, placebo-controlled, crossover trial.</td>
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<td>A randomized, controlled trial of oxycodone versus placebo in patients</td>
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eTable 2. Reporting of patient-important outcome domains in protocols and papers of eligible studies

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<th>Study</th>
<th>IMMPACT-recommended patient-important outcome domain</th>
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<tr>
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<td>Paper</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>Paper</td>
<td>+</td>
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<td>+</td>
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<td>14</td>
<td>Protocol</td>
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<td>Paper</td>
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</table>

(+) 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:


Wolters Kluwer Health, Lippincott Williams & Wilkins ©
Management of central post-stroke pain: a systematic review of randomized controlled trials

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Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada

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Cover title: Management of central post-stroke pain

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

Word count: 5,482
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.\textsuperscript{1} The pain may be spontaneous, occurring either constantly or intermittently, or evoked in response to external stimuli.\textsuperscript{1} It may develop immediately after a stroke, or years later.\textsuperscript{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.\textsuperscript{6} Because CPSP case definition is complex,\textsuperscript{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.\textsuperscript{4} Individuals with CPSP commonly experience sensory abnormalities, including increased tactile and thermal sensitivities, which impair their quality of life.\textsuperscript{7-9} The underlying mechanisms of CPSP are poorly understood,\textsuperscript{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.\textsuperscript{10-12} The available reviews suffer from important limitations,\textsuperscript{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.\textsuperscript{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.\textsuperscript{17} We used an online systematic review software application (DistillerSR\textsuperscript{TM}, 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. 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. 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. 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.

**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. 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.

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. Using this approach, RCTs begin as high certainty but can be rated down due to: (1) risk of bias; (2) inconsistency; (3) indirectness; (4) imprecision; and, (5) publication bias. 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. 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.

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).\(^\text{37-44}\) 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.\(^\text{41}\) 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,\(^\text{37, 40-42}\) 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 \textit{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.\textsuperscript{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).

\textbf{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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 acupuncture 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, and we are further validating this hypothesis in an ongoing network meta-analysis of all therapies for all chronic neuropathic pain conditions.

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.
Acknowledgements

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

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.
References


17. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33:159-174


Figure 1. Study flow chart

8,400 records identified through database searching

3,385 records after duplicates removed

5,015 records screened 4,691 records excluded

316 full-text articles excluded:
Did not randomize participants (n=165)
Did not address a therapeutic research question (n=4)
Did not enrol participants with central post-stroke pain (n=125)
Did not enrol at least 10 participants (n=13)
Did not follow up participants for at least 2 weeks (n=9)

324 full-text articles assessed for eligibility

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

Table 1. Characteristics of eligible studies
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Intervention Details</th>
<th>Duration</th>
<th>Median Age</th>
<th>Female</th>
<th>Male</th>
<th>Median Duration</th>
<th>Female</th>
<th>Male</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Jungehulsing et al. | Germany         | Crossover | 1) Levetiracetam (3000 mg/day, maximum dose)  
2) Placebo                             | 8 weeks (2 weeks washout)             | 42          |        |      | 61.5 years     | 16     | 26    | 40-76 1 participants withdrew due to protocol violations  
1 participants withdrew consent  
3 participants withdrew due to adverse events |
| Hosami et al.    | 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   | 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.       | Republic of Korea | Parallel  | 1) Acupuncture (0.05 mL)  
2) Saline Acupuncture                       | Twice weekly, 3 weeks                 | 20          |        |      |                 |        | 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)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Anticonvulsant</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Leijon et al. 17</td>
<td>3.56</td>
<td>1.89</td>
<td>14</td>
<td>4.78</td>
</tr>
<tr>
<td>Vestergaard et al. 19</td>
<td>5</td>
<td>2.22</td>
<td>27</td>
<td>7</td>
</tr>
<tr>
<td>Kim et al. 15</td>
<td>4.9</td>
<td>2.08</td>
<td>110</td>
<td>5</td>
</tr>
<tr>
<td>Jungheusing et al. 27</td>
<td>7</td>
<td>2.96</td>
<td>33</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>184</strong></td>
<td><strong>100.0%</strong></td>
<td>-0.75 [-1.71, 0.21]</td>
<td>-0.75 [-1.71, 0.21]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.63; \quad \chi^2 = 9.63, \quad df = 3 (P = 0.02); \quad I^2 = 69\%$

Test for overall effect: $Z = 1.54 (P = 0.12)$
Figure 4B. Effects of anticonvulsants versus placebo on any adverse events

<table>
<thead>
<tr>
<th>Study</th>
<th>Anticonvulsant</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Leijon et al.97</td>
<td>13</td>
<td>14</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Vestergaard et al.</td>
<td>17</td>
<td>30</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>Kim et al.41</td>
<td>57</td>
<td>110</td>
<td>25</td>
<td>109</td>
</tr>
</tbody>
</table>

Total (95% CI) 154 154 100.0% 1.61 [0.90, 2.88]

Total events 87 50

Heterogeneity: Tau² = 0.21; Chi² = 9.83, df = 2 (P = 0.007); I² = 80%
Test for overall effect: Z = 1.61 (P = 0.11)
Table 2. GRADE Evidence Profile: Anticonvulsants vs. Placebo

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>№ of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Pain intensity (follow up: range 4 to 12 weeks; assessed with: Visual Analogue Scale; 0 (no pain) to 10 (worst pain))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>randomised trials</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Any adverse event (follow up: range 4 to 12 weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>randomised trials</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Depression (follow up: range 4 to 12 weeks; assessed with: Various instruments)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>randomised trials</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Patient-reported global improvement (follow up: 12 weeks; assessed with: Patient Global Impression of Change; 1 (very much improved) to 7 (very much worse))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomised trial</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Sleep (follow up: 12 weeks; assessed with: Sleep Problems Index, Medical Outcomes Study Sleep Scale; 0 (no problems) to 100 (most severe problems))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomised trial</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

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:


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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 I² 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 than 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. 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 \textit{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:

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 (Guillain 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)
exp Herpes Zoster/ (9636)  
postherpetic.mp. (1800)  
Diabetic Neuropathies/ (12033)  
small fiber.mp. (716)  
exp HIV/ (84444)  
hiv.mp. (275179)  
or/1-65 (1625784)  
neuropath*.mp. (102493)  
neuralgi*.mp. (18296)  
facial pain/ (5019)  
phantom limb/ (1528)  
phantom limb.mp. (1828)  
CRPS.ti,ab. (1390)  
CPSP.ti,ab. (157)  
burning mouth syndrome/ (732)  
dysesthe*.ti,ab. (1613)  
(chronic adj2 pain).ti,ab. (31746)  
pain measurement/ (60773)  
or/67-77 (201452)  
66 and 78 (119454)  
Trigeminal Neuralgia/ (5540)  
Facial Neuralgia/ (1121)  
Facial Pain/ (5019)  
Glossalgia/ (247)  
Burning Mouth Syndrome/ (732)  
Trigeminal Autonomic Cephalalgias/ (105)  
nervalgia/ or neuralgia, postherpetic/ or piriformis muscle syndrome/ or pudendal neuralgia/ or sciatica/ (12818)  
nervalgi*.mp. (18296)  
Post-mastectomy pain.mp. (27)  
postmastectomy pain syndrome.mp. (24)  
PMPS.mp. (406)  
Post-thoracotomy pain.mp. (234)  
Phantom limb.mp. (1828)  
agnosia.mp. (2575)  
Glossodynia.mp. (136)  
Stomatodynia.mp. (45)  
tic adj do?lo?re?ux?).mp. (300)  
Proxopalgia.mp. (15)  
meralgia paresthetica.mp. (277)  
metatarsalgia.mp. (566)  
(Ramsay adj hunt).mp. (440)  
odontalgia.mp. (151)  
sciatica.mp. (5358)
(Pain adj2 clinic).ti,ab. (1417)
(chronic adj2 pain).ti,ab. (31746)
(Neurogen* adj2 pain).ti,ab. (429)
low back pain/ (14091)
or/80-106 (77534)
79 or 107 (176257)
(dh or dt or pc or rh or rt or su or th).fs. (5395344)
exp Analgesia/ (31987)
exp Analgesics/ (433810)
analges*.mp. (140770)
treat*.mp. (4077132)
therap*.mp. (2410630)
intervention*.mp. (583724)
manag*.mp. (963377)
or/109-116 (8422296)
108 and 117 (104367)
randomized controlled trial.pt. (376906)
controlled clinical trial.pt. (88589)
randomized.ab. (297403)
placebo.ab. (155216)
drug therapy.fs. (1709609)
randomly.ab. (215113)
trial.ab. (308899)
groups.ab. (1367352)
or/119-126 (3364472)
exp animals/ not humans.sh. (3955572)
127 not 128 (2886355)
118 and 129 (36678)
limit 130 to "therapy (maximizes sensitivity)" (30615)
limit 131 to "review articles" (6311)
131 not 132 (24304)
Transcranial Magnetic Stimulation/ (6992)
rtms.mp. (2511)
magnetics/tu (807)
134 or 135 or 136 (8481)
pain.mp. (480976)
137 and 138 (542)
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, angiookeratoma 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 neuralgia
  - 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 mastectomy pain 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 ophthalmoplegia;
  - 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

136
- 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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6Department of Medicine, McMaster University, Hamilton, Ontario, Canada
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. 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 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. 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 $\geq 0.20$ 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 $\geq 0.20$ across the different models, we presented the effect sizes from the overall (pooled) model; if the HRs varied by $\geq 0.20$, 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.\textsuperscript{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.

\textit{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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Competing interests: All authors report no conflicts of interest.
REFERENCES


7. Canada S. Days lost per worker due to illness or disability, by sex, by province (Both sexes). 2015; [http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health47a-eng.htm](http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health47a-eng.htm).


Table 1. Description of variables

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

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>STD, n(%)</th>
<th>LTD, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total claimants</td>
<td>70776</td>
<td>22205</td>
</tr>
<tr>
<td>Age: Median (Q1 to Q3) years</td>
<td>46 (36 to 53)</td>
<td>48 (40 to 54)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31068 (43.9%)</td>
<td>10052 (45.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>39708 (56.1%)</td>
<td>12153 (54.7%)</td>
</tr>
<tr>
<td>Monthly salary: Median (Q1 to Q3)</td>
<td>$3695.5 ($2915.5 to $4546.5)</td>
<td>$3521.8 ($2799.8 to $4546.5)</td>
</tr>
<tr>
<td>Job demands</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>22586 (31.9%)</td>
<td>8104 (36.5%)</td>
</tr>
<tr>
<td>Light</td>
<td>30217 (42.7%)</td>
<td>8604 (38.8%)</td>
</tr>
<tr>
<td>Heavy</td>
<td>17973 (25.4%)</td>
<td>5497 (24.8%)</td>
</tr>
<tr>
<td>Province</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quebec</td>
<td>59117 (83.5%)</td>
<td>16700 (75.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>11659 (16.5%)</td>
<td>5505 (24.8%)</td>
</tr>
<tr>
<td>Illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological disorder</td>
<td>15294 (21.6%)</td>
<td>7325 (33.0%)</td>
</tr>
<tr>
<td>Musculoskeletal disease</td>
<td>22124 (31.3%)</td>
<td>7165 (32.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>33358 (47.1%)</td>
<td>7715 (34.7%)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10381 (14.7%)</td>
<td>6447 (29.0%)</td>
</tr>
<tr>
<td>No</td>
<td>60395 (85.3%)</td>
<td>15758 (71.0%)</td>
</tr>
<tr>
<td>Receipt of SSQ Financial-facilitated IME*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>----------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Yes</td>
<td>1341 (1.9%)</td>
<td>2275 (10.3%)</td>
</tr>
<tr>
<td>No</td>
<td>64435 (98.1%)</td>
<td>19930 (89.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Receipt of SSQ Financial-funded rehabilitation*</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>1098 (1.6%)</td>
<td>2552 (11.5%)</td>
</tr>
<tr>
<td>No</td>
<td>69678 (98.5%)</td>
<td>19653 (88.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time to claim approval: Median (Q1 to Q3) weeks</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0 (0.9 to 1.9)</td>
<td>2.4 (1.1 to 5.6)</td>
</tr>
</tbody>
</table>


*At some point during benefits period.
Table 3. Determining factors predictive of time to short-term disability benefits duration based multivariable Cox regression analysis

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

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

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

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

<table>
<thead>
<tr>
<th>Predictor</th>
<th>STD</th>
<th>LTD</th>
<th>Anticipated direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Higher salary</td>
<td>-</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Female (versus males)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Heavy job demands (versus sedentary)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Light job demands (versus sedentary)</td>
<td>NS</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Quebec residency (versus else)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of comorbidity (versus no comorbidity)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Attending an IME (versus not attending an IME)</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Receipt of rehabilitation (versus no receipt of rehabilitation)</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Longer time to claim approval</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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.