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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Intravenous Lidocaine for Chronic Pain: A Review of the Clinical Effectiveness and Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Context and Policy Issues

Chronic pain, defined as lasting at least three to six months after onset,[1] remains a major problem in Canada and worldwide.[2,3] In 2011, it was estimated that almost 19% of Canadians were suffering from chronic pain,[2] with similar estimates worldwide.[3] Chronic pain affects the individual's quality of life, daily activities, workplace and social activities, relationships with family members who often assume caregiver roles, and other social contacts.[4]

Lidocaine is an antiarrhythmic agent (Class Ib, Fast Sodium Channel Blocker)[5] given intravenously to treat pulseless ventricular tachycardia or ventricular fibrillation to help restore a normal cardiac rhythm.[6] Lidocaine is also used as a local injection to treat pain at the site (e.g., trigger point therapy).[7,8] There has been interest in the use of intravenous lidocaine as a treatment for chronic pain.[9] Recent papers have demonstrated the effectiveness of intravenous lidocaine in decreasing pain perioperatively.[10,11] Intravenous lidocaine is associated with serious side effects including bradycardia, cardiac arrhythmias, circulatory shock, coronary artery vasospasm, heart blocks, coma, anaphylaxis, hypersensitivity reactions, bronchospasm, dyspnea, respiratory depression and many others, precipitating the need for electrocardiogram monitoring.[6]

The purpose of this Rapid Response is to collect, critically appraise and evaluate the current evidence on the clinical effectiveness and adverse effects of intravenous lidocaine in treating chronic pain, as well as to review recent evidence-based guidelines for its use in patients with chronic pain.

Research Questions

1. What is the clinical effectiveness of intravenous lidocaine for chronic pain?

2. What are the evidence-based guidelines on the use of intravenous lidocaine for chronic pain?

Key Findings

Evidence from two systematic reviews was limited in quality and quantity and addressed a wide range of causes of chronic pain. The findings were inconsistent and limited the ability to draw firm conclusions about the effectiveness of intravenous lidocaine for chronic pain.

Relevant evidence from one of two identified guideline documents was more useful. Although both guideline documents were published in 2012, one set of guidelines provided a Grade B recommendation on the use of intravenous lidocaine for neuropathic pain but with evidence lacking in certain areas. The other guideline considered one study of intravenous lidocaine and did not support the use of intravenous lidocaine in the recommendation for the management of fibromyalgia.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, Medline, EMBASE, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as

a focused Internet search. No methodological filters were added to retrieve articles by study type. The search was also limited to English language documents published between January 1, 2012 and December 20, 2017.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with chronic pain
Intervention	Intravenous lidocaine (e.g., infusion, bolus)
Comparator	Q1: Other pain treatments, placebo (comparator for randomized controlled trials only) Q2: No comparator
Outcomes	Q1: Clinical effectiveness (benefit/harm), safety Q2: Guidelines
Study Designs	Q1: Health Technology Assessments, Systematic Reviews, Meta-Analyses, Randomized Controlled Trials, Non-Randomized Studies Q2: Guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or they were published prior to 2012. Case histories, case series, non-systematic reviews and guidelines with unclear methodology were excluded. Articles were excluded if they assessed the effect of topical lidocaine, lidocaine injections (including nerve blocks, Bier blocks) and oral lidocaine. Articles were also excluded if they did not evaluate treatment of chronic pain.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR 2 tool[12] and guidelines were appraised with the AGREE II tool.[13] Summary scores were not calculated for the included studies, rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 368 citations were identified in the literature search. Following screening of titles and abstracts, 329 citations were excluded and 39 potentially relevant reports from the electronic search were retrieved for full-text review, and 18 potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 53 publications were excluded for various reasons, and four publications met the inclusion

criteria and were included in this report. These comprised two systematic reviews, and two evidence-based guidelines. There were no eligible randomized controlled trials or non-randomized studies found. Appendix 1 describes the PRISMA flowchart of the review.[14]

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Two systematic reviews were included, Laoire and Murtagh[15] which was published in 2017, and van der Wal et al.[16] which was published in 2016. Laoire and Murtagh[15] evaluated pharmacological therapies used to treat critical limb ischemia which could not be treated surgically or by using invasive procedures. The review[15] included studies published between 1996 and 2006, including all study designs except for case studies. There was one included study addressing the effect of intravenous lidocaine on chronic pain in critical limb ischemia.

The review by van der Wal et al.[16] was published in 2016 and evaluated in vitro and clinical (animal and human) studies that reported the neuroinflammatory response from lidocaine, and used pain as the outcome for clinical human studies published between July 1975 and August 2014. The human studies considered reviews, randomized trials, prospective studies and retrospective studies for inclusion. There were 11 clinical human studies which evaluated the effect of intravenous lidocaine on chronic pain; one study was a systematic review, six studies were randomized crossover design trials and four studies were single-arm retrospective studies.

There was no overlap in the included studies relevant for this report in these two reviews. Additional information for both reviews is available in Appendix 2, Table 2.

Two guidelines[17,18] targeted a range of treatments by health professionals for specific conditions, fibromyalgia and neuropathic pain respectively. Fitzcharles et al.[17] published the fibromyalgia guidelines in 2012. The authors did not specify the study designs used to inform the guidelines, conducting a search in five databases from 1990 to 2010. The evidence was graded using the classification system of the Oxford Centre for Evidence Based Medicine[19] and recommendations were voted on by the National Fibromyalgia Guidelines Advisory Panel. One study in these guidelines was relevant to this report and the study characteristics reported are the number of subjects (75) and the duration of follow-up (four weeks). There is no reporting of study design, and no discussion of any biases and subsequent grading of this study.

Mailis and Taenzer[18] published guidelines on different treatments for neuropathic pain in 2012. The authors searched for systematic reviews, randomized trials and guidelines published between January 1997 and May 2008. The search strategies, including key words and the databases searched were not reported and are not available online. Grading the evidence was conducted using a modified version of the US Preventive Services Task Force grading system.[18] Evidence was assessed using a consensus process. There are 14 included studies (three systematic reviews, 11 randomized controlled trials) on intravenous infusions of any medication. It was not reported how many studies report on the effect of intravenous lidocaine. The full guideline that evaluates intravenous interventions is not available online.

Additional information for both the Fitzcharles et al.[17] and the Mailis and Taenzer[18] guidelines is available in Appendix 2,Table 3.

Country of Origin

The two systematic reviews[15,16] were led by authors based in Ireland and the Netherlands respectively. The two guidelines[17,18] were carried out by Canadian teams and targeted Canadian populations.

Patient Population

In the systematic review by Laoire and Murtagh,[15] the patients were required to have critical limb ischemia according to The Inter-Society Consensus for the Management of Peripheral Arterial Disease, defined as "*any patient with chronic ischemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease*" (p. 1). For the study in this review evaluating intravenous lidocaine, the setting was an emergency department in a tertiary referral centre.

In the van der Wal et al. paper,[16] there were 11 relevant studies addressing subjects with chronic pain. Conditions treated included pain from spinal cord injury, multiple sclerosis, nerve injuries, failed back surgery and cancer. Settings were not specified in the relevant studies.

Fitzcharles et al.[17] specified that the guidelines were developed for diagnosing and treating patients with fibromyalgia. The guidelines published by Mailis and Taenzer[18] targeted adult patients with neuropathic pain. Settings were not specified in either guideline.

Interventions and Comparators

The Laoire and Murtagh review[15] evaluated the effect of any pharmacological interventions to treat critical limb ischemia. There was one included study evaluating intravenous lidocaine. The study was a randomized controlled trial, comparing the effect of lidocaine at a dose of two milligrams per kilogram of body weight (mg/kg) intravenous over five minutes. The comparator group was given an intravenous dose of morphine of 0.1 mg/kg over five minutes. The number of doses was not reported in the systematic review.

The van der Wal et al. review[16] included 11 studies that evaluated the effect of intravenous lidocaine on chronic pain: one systematic review, six randomized crossover design trials and four non-randomized studies. The systematic review included 16 studies of intravenous lidocaine (not including studies of combination therapies) with dosages of intravenous lidocaine ranging from one mg/kg to five mg/kg. The duration of the dose was not reported other than a constant rate of infusion, and comparators were not reported. The six randomized crossover design trials included dosages of intravenous lidocaine ranging from one mg/kg to 7.5 mg/kg, with durations of the dose ranging from 30 minutes to six hours. Three crossover trials included one dose of intravenous lidocaine, two crossover trials included two different doses of intravenous lidocaine, and one crossover trial included three different dosages. Of the three studies with multiple doses, two studies reported on the effect of one specific dosage; two of the three also provide general effectiveness statements. Five of the six crossover trials used saline as a comparator; the remaining trial did not specify the placebo. Two of the six crossover trials had additional comparators; one trial had a comparator of 322 mg of NS1209 (a treatment for pain not otherwise defined) given intravenously. One trial assessed the effect of ketamine compared to saline which is out of the scope of this report. There were four single-arm retrospective studies in the

review by van der Wal et al.,[16] with the dosages of intravenous lidocaine ranging from one to five mg/kg/hour with a constant rate of infusion.

The Fitzcharles et al. fibromyalgia guidelines[17] evaluated any treatments used for fibromyalgia. Treatment categories reported include non-pharmacologic treatment, self-management strategies, multicomponent therapy, psychological interventions, and others. Intravenous lidocaine was evaluated as one of the pharmacologic treatments but dosage, duration and comparators were not reported.

The guidelines on neuropathic pain[18] evaluated any treatment used for neuropathic pain. Intervention categories included spinal cord stimulation, intravenous infusions, epidural injections and nerve blocks. There were 14 included studies on intravenous infusions, but it was not reported how many of these studies report on the effect of intravenous lidocaine and which comparators were used.

Outcomes

The systematic review by Laoire and Murtagh[15] included one study that measured the effect of intravenous lidocaine on pain using a visual analogue scale. A lower score on the scale represented a decrease in pain 30 minutes after starting the intravenous lidocaine. The subjects were monitored for 30 minutes for adverse events.

The van der Wal et al.[16] review included 11 studies assessing humans with pain as an outcome. The methods of measuring pain were not reported in the one included systematic review and many of the other studies. The randomized controlled trials in this review used a variety of methods to measure pain including brush evoked pain, allodynia, and pin prick hypersensitivity. Duration of pain as an outcome was reported in two studies, ranging from four hours to 28 days. A numerical rating scale was used to measure pain in two of the four retrospective studies. Adverse events were reported in the systematic review, one of the randomized controlled trials and one of the retrospective studies.

Both guidelines report on pain outcomes for lidocaine treatment. Fitzcharles et al.[17] does not specify how pain was measured in the one relevant study in their guidelines. Mailis and Taenzer[18] describes pain relief duration ranging from a few hours to four weeks, but no reporting of how pain was measured.

Summary of Critical Appraisal

The systematic reviews were critically appraised using the AMSTAR 2 tool.[12] Both systematic reviews[15,16] provided a clear research question, searched multiple databases, and reported their own funding situation for the review. Laoire and Murtagh[15] included a list of excluded studies and carried out a full risk of bias assessment for the included studies, graded the evidence, and considered the grading in the conclusions.[20] There was no risk of bias assessment in the van der Wal et al. review.[16] Neither systematic review indicated that they had prepared a protocol in advance of the review; a protocol ensures that methods have been considered prior to carrying out the review, minimizing the bias in the conduct of the review.[12,21] Neither systematic review indicated the use of duplicate study selection or extraction to minimize errors and reduce author biases.[21] Additional details regarding the strengths and limitations of both systematic reviews are provided in Appendix 3, Table 4.

Both guidelines[17,18] met most of the criteria for the AGREE II assessment tool.[13] Although both guidelines[17,18] described methods for grading identified evidence, neither discussed

the strengths and limitations of the evidence specifically found on the effectiveness of intravenous lidocaine on chronic pain in fibromyalgia. Mailis and Taenzer18 did not report seeking the input of the target population and it was not possible to fully assess if systematic methods were used for the literature search. Mailis and Taenzer18 did not address any of the items in the AGREE II Applicability domain, nor did they indicate a plan for updating the guideline. Fitzcharles et al.[17] indicated that the guidelines would be updated in 2015 but no updated guidelines were identified in the CADTH literature searches. Additional details regarding the strengths and limitations of both guidelines are provided in Appendix 3, Table 5.

Summary of Findings

What is the clinical effectiveness of lidocaine for chronic pain?

Two systematic reviews were identified evaluating lidocaine for chronic pain.[15,16] The scope of the Laoire and Murtagh review[15] was to address the effectiveness of different treatments for ischemic pain for those patients with critical limb ischemia. The authors identified one randomized controlled trial evaluating intravenous lidocaine for critical limb ischemia, with 20 patients in each arm. The group that received lidocaine had less pain as measured by a visual analog scale than the group that received morphine at 15 minutes and at 30 minutes post treatment. No adverse events were reported within a 30 minute follow-up.

The van der Wal et al. review[16] evaluated the effect of intravenous lidocaine on any condition causing chronic pain. One of the included studies in the van der Wal et al. review[16] was a systematic review with 16 trials addressing the effect of intravenous lidocaine. The van der Wal et al.[16] authors report that intravenous lidocaine "tended to be more effective for relieving neuropathic pain caused by diabetes, trauma or cerebrovascular diseases" (p. 668-9). No serious side effects were reported but minor side effects were present in 35% of the patients receiving intravenous lidocaine, compared to 12% in the placebo arms.

The remaining ten studies which addressed intravenous lidocaine used in humans in the van der Wal et al. review[16] were six randomized crossover design trials and four retrospective single-arm studies. The crossover trials assessed treatment of chronic pain in a variety of conditions, including chronic neuropathic pain, fibromyalgia, diabetic neuropathy, and failed back surgery. Four of the six crossover trials had saline as the comparator, one had an undefined placebo and one had both saline and NS1209 (a treatment for pain not otherwise defined) as comparators.

Of the six crossover randomized controlled trials with comparisons to saline or placebo, two showed all outcomes favouring lidocaine (one had mild adverse events which were not specified), three crossover trials had mixed results depending on the outcomes measured, and one crossover trial had reduction of pain in both groups. The study that also compared intravenous lidocaine to NS1209, found that both treatments had the same effects. Of the three studies assessing multiple dosages of intravenous lidocaine, one study reported the effect of the highest dosage, one study reported on the increased benefit of the higher dose and a statement overall on the effect of intravenous lidocaine and the third study reported a general statement of effect.

The four retrospective studies demonstrated a decrease in pain from baseline levels from the intravenous lidocaine treatment with mild or moderate side effects.

Additional details regarding the comparisons and results of both reviews are provided in Appendix 4, Table 6.

What are the evidence-based guidelines on the use of intravenous lidocaine for chronic pain?

Two guidelines were identified in the literature searches for this Rapid Response report. Both of them assessed multiple interventions. The guidelines by Fitzcharles et al.[17] included one study evaluating intravenous lidocaine for fibromyalgia showing a moderate effect in pain relief after four weeks. However, lidocaine was not mentioned in the corresponding recommendation. Pregabalin and duloxetine were the two medications supported in the corresponding medication as they were the two medications not considered 'off-label' by Health Canada for symptom management in fibromyalgia at the time. The other medications, including intravenous lidocaine, were not described in a recommendation. The recommendation is quoted in Appendix 4, Table 7.

The Mailis and Taenzer guidelines[18] recommend that intravenous lidocaine could be useful in patients with neuropathic pain who have not benefitted from other pharmacological treatments, with dosages ranging from five to 7.5 milligrams per kilogram of body weight for a few hours to four weeks of pain relief. The authors judge this recommendation be Grade B ("*B: Recommend. High certainty with moderate effect or moderate certainty with moderate to substantial effect.*" p. 152).[18] The authors do not report on adverse effects or how they determined the dosage recommendations but they do report that there are no data on repeat infusions.

Appendix 4 presents the relevant recommendations from each guideline.

Limitations

The systematic reviews and evidence-based guidelines identified for this report had limitations which may have impacted our findings. The lack of risk of bias assessment of the included studies in the van der Wal et al. review[16] limits our assessment of the usefulness of the findings. The Laoire and Murtagh review[15] had few quality limitations according to AMSTAR 2[12] but focused on the evidence on the effectiveness of intravenous lidocaine for pain in people with critical limb ischemia, and the Fitzcharles et al. guidelines[17] focused on fibromyalgia, thus limiting their generalizability to other chronic pain conditions. Finally, the Mailis and Taenzer guidelines[18] did identify a larger number of trials assessing the effect of intravenous lidocaine on neuropathic pain, but the exact number of studies reporting on lidocaine and study characteristics were not presented in detail.

There are many gaps in the evidence regarding the use of intravenous lidocaine for the treatment of chronic pain. Many of the individual studies within the reviews and guidelines had short follow-up periods, some studies had less than an hour of follow-up[15] with very few studies having more than a week of follow-up.[16] As noted in the van der Wal et al. review,[16] there is a range of dosages, schedules, and outcomes used to evaluate the effects of intravenous lidocaine on chronic pain. Consistent treatment protocols and standardized outcome measures might provide more useful data to facilitate addressing this important research question. As described by Mailis and Taenzer[18] in their guideline, evidence is needed on outcomes from courses of treatment with multiple doses of the drug over months or longer.

It is not reasonable to apply the results of the two disease specific systematic reviews or guidelines to other conditions. There are multiple diseases and conditions which are

associated with chronic pain for which intravenous lidocaine has been used, as noted in the van der Wal et al. review.[16] Both guidelines were carried out by Canadian groups; some of the recommendations may not be as pertinent in other countries. For example, recommended cardiac monitoring equipment necessary while intravenous lidocaine is being administered to recognize adverse events will likely affect the expense and the availability of this treatment.[6]

Conclusions and Implications for Decision or Policy Making

Two systematic reviews were identified to address the first research question and two guidelines were identified to address the second research question.

The evidence presented is limited in quantity and quality for using intravenous lidocaine to treat chronic pain. The van der Wal et al. review[16] reported multiple studies of intravenous lidocaine for a range of conditions and the results were inconsistent, even within individual studies where multiple assessments of pain were used. The one individual study assessing intravenous lidocaine in the Laoire and Murtagh[15] review was insufficient to provide a strong conclusion on the treatment of lidocaine for critical limb ischemia. Both systematic reviews recognized the need for more research.[15,16] One guideline[18] was lacking in the descriptive detail including number of studies, but did provide a Grade B recommendation supporting intravenous lidocaine. One of the pharmacological recommendations from the fibromyalgia guideline pointed out that in 2012 when the guideline was written, there were two drugs approved by Health Canada for treatment of fibromyalgia and neither one was lidocaine. It is possible that this lack of approval of intravenous lidocaine for fibromyalgia contributed to the lack of identified evidence in fibromyalgia, and possibly in other conditions as well.

Future research is required to determine the effect of intravenous lidocaine on specific conditions causing chronic pain, standard dosing and long term follow-up with monitoring of adverse events to ensure reasonable confidence in decisions whether to treat chronic pain with intravenous lidocaine.

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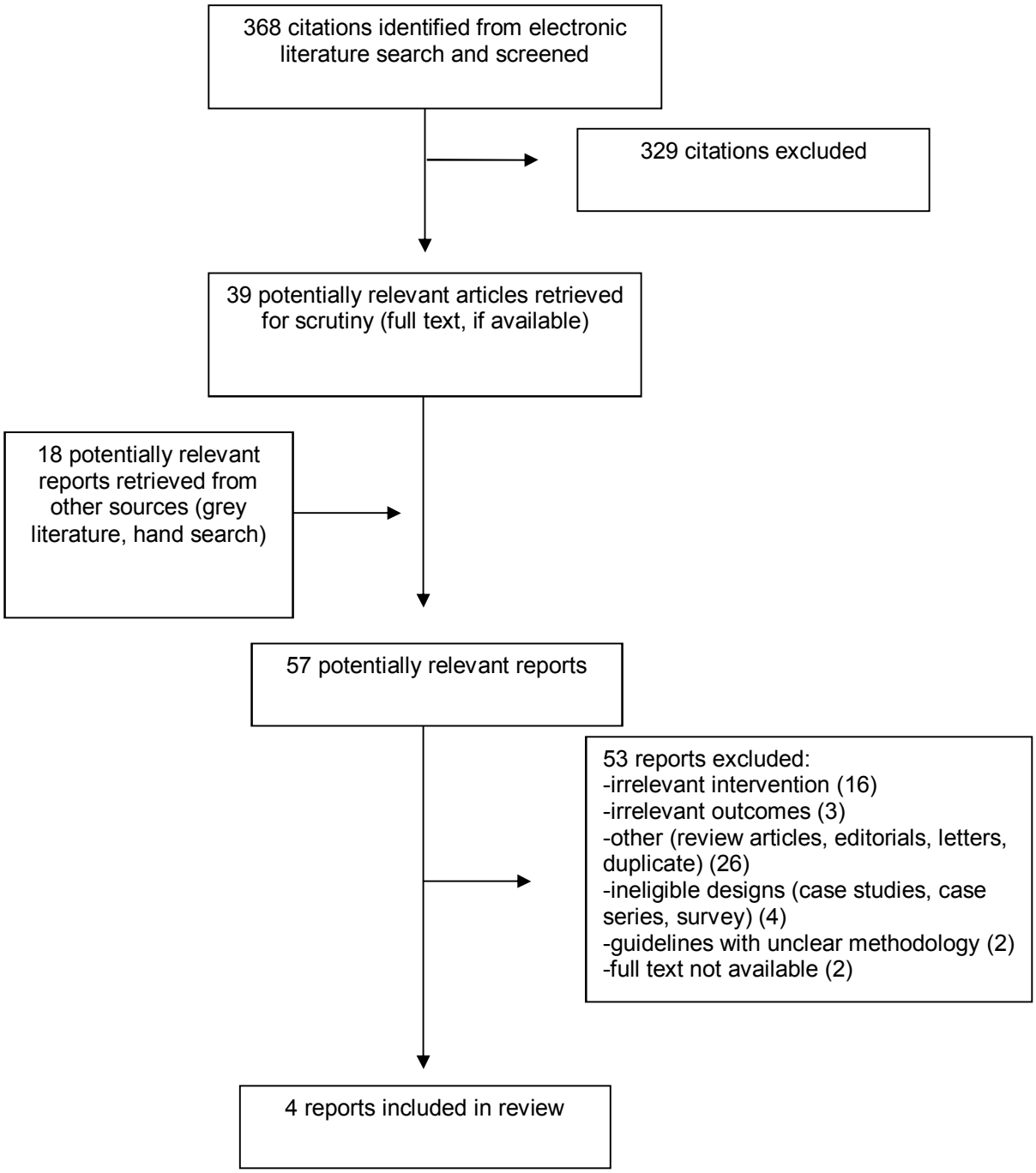
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Laoire and Murtagh, 2017, Ireland[15]	All study designs except for case studies; one study relevant to lidocaine research question	Patients with critical limb ischemia	Intervention: Intravenous lidocaine Comparator: Intravenous morphine	Outcome: Visual analogue scale for pain, monitored for adverse effects. Measurements pre-infusion, 15 minutes and 30 minutes post infusion
van der Wal, 2016, The Netherlands[16]	88 studies in total but 11 relevant studies to the research question: one Cochrane systematic review, six crossover randomized controlled trials, four retrospective single-arm studies	Patients suffering with chronic pain. No age or specific disease restrictions	Intervention: Lidocaine intravenous or bolus, doses ranging from 1mg/kg to 7.5 mg/kg, duration of dose varies from 30 minutes to 6 hours, not fully described in 6/11 studies, duration of constant rate of infusion is not reported. Comparators: Saline, NS1209 (a treatment for pain not otherwise defined), placebo, no comparators for retrospective studies	Outcomes: Pain measured by pin prick, brush evoked and spontaneous pain, allodynia (cold, thermal and mechanical), hyperalgesia, numerical rating scales and inflammatory components of complex regional pain syndrome. Method of pain measurement not reported in review, three crossover trials, and two retrospective studies. Adverse effects reported in systematic review, one crossover trial and four retrospective studies. Follow-up ranged from 4 hours to 3 months; not reported in 7 of the studies

mg/kg = milligrams of drug per kilogram of body weight.

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
2012 Canadian Guidelines for the Diagnosis and Management of Fibromyalgia Syndrome, Fitzcharles et al.[17]						
The guideline is intended for any healthcare professionals in Canada, who treat patients with fibromyalgia and also useful for patients with fibromyalgia	Both diagnosis and management of fibromyalgia are reported in this guideline. Management includes pharmacological interventions (including lidocaine and many others) and non-pharmacological approaches such as complementary medicine, exercise and self-management strategies	Outcomes were not considered a priori, but were identified as part of the process of evaluating the evidence. Outcomes cited within these guidelines include pain, function, quality of life, and other symptoms. The outcome reported for intravenous lidocaine study was pain, method not described..	A needs assessment from health professionals treating fibromyalgia, followed by searches of 5 databases (EMBASE, MEDLINE, PSYCHINFO, PUBMED, and Cochrane Library) from 1990 to 2010 with additional manual searches of references.	The classification system of the Oxford Centre for Evidence Based Medicine was used to grade the evidence.[19] Treatments were classified as Level 1 (systematic reviews of randomized controlled trials or n-of-1 trials) to Level 5 (opinion) based on the strength of the supporting evidence. Resulting recommendations were graded as Grade A (consistent Level 1 studies) to Grade D (Level 5 evidence or troublingly inconsistent or inconclusive studies of any level) or Consensus (Opinion supported by entire Canadian Fibromyalgia Guidelines Committee).	Recommendations were circulated to the Canadian Fibromyalgia Guidelines Committee initially and then to the National Fibromyalgia Guidelines Advisory Panel, revised and recirculated. Canadian Pain Society also evaluated the guidelines using the AGREE II tool.[13]	Internal and external peer review

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Evidence-based guideline for neuropathic pain interventional treatments: Spinal cord stimulation, intravenous infusions, epidural injections and nerve blocks, Mailis and Taenzer 2012[18]						
Target audience: Physicians and health care teams involved in the diagnosis and management of neuropathic pain. Target population is adults with neuropathic pain of various etiologies.	A Canadian Pain Society survey was carried out to assess members' views on which treatments, other than oral medications, are most important for neuropathic pain. Intravenous infusions were one of the identified treatments.	Studies were included that treated neuropathic pain.	Systematic reviews, randomized controlled trials and clinical practice guidelines published in English from January 1997 to May 2008. Narrative description of studies in paper	Modified US Preventive Services Task Force tool.[18] The USPSTF tool includes three elements: 1. Quality of evidence used (good, fair, or poor) 2. Certainty with regard to quality of evidence (high, moderate, or low) 3. Grade of recommendations: • A & B: recommend • C: may recommend • D: recommend against • I: insufficient evidence to make recommendation	Preliminary recommendations drafted and circulated internally and externally	Internal and external peer review

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews using AMSTAR 2[12]

Strengths	Limitations
Laoire and Murtagh, 2017,[15]	
• Clear research question • Included multiple databases • Included a list of excluded studies • Details provided for included studies • Risk of bias assessment done with grading • Appropriate decision not to meta-analyze all studies due to heterogeneity reported. • Author's funding situation reported	• No protocol • No explanation for study design inclusion • No expert consultation for searches • No evidence of duplicate study selection or data extraction • No sources of support of included studies reported
van der Wal, 2016[16]	
• Clear research question • Searched multiple databases • Appropriate decision not to meta-analyze all studies due to heterogeneity but not reported or discussed • Author's funding situation reported	• No protocol • No explanation for study design inclusion • Limitations in literature search • No evidence of duplicate study selection or data extraction • No list of excluded studies • Details missing in included study descriptions • No risk of bias assessment of included studies • No sources of support of included studies reported • No discussion of heterogeneity

Table 5: Strengths and Limitations of Guidelines using AGREE II[13]

Item	Guideline	
	Fitzcharles et al., 2012[17]	Mailis and Taenzer, 2012[18]
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	✓	✓
2. The health question(s) covered by the guideline is (are) specifically described.	✓	✓
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	✓	✓
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	✓	✓
5. The views and preferences of the target population (patients, public, etc.) have been sought.	✓	X
6. The target users of the guideline are clearly defined.	✓	✓
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	✓	X
8. The criteria for selecting the evidence are clearly described.	✓	✓
9. The strengths and limitations of the body of evidence are clearly described.	X	✓
10. The methods for formulating the recommendations are clearly described.	✓	✓
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	✓	X
12. There is an explicit link between the recommendations and the supporting evidence.	✓	X
13. The guideline has been externally reviewed by experts prior to its publication.	✓	✓
14. A procedure for updating the guideline is provided.	X	X
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	✓	✓
16. The different options for management of the condition or health issue are clearly presented.	✓	✓
17. Key recommendations are easily identifiable.	✓	✓
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	✓	X
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	✓	X

Table 5: Strengths and Limitations of Guidelines using AGREE II[13]

Item	Guideline	
	Fitzcharles et al., 2012[17]	Mailis and Taenzer, 2012[18]
20. The potential resource implications of applying the recommendations have been considered.	X	X
21. The guideline presents monitoring and/or auditing criteria.	✓	X
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	✓	✓
23. Competing interests of guideline development group members have been recorded and addressed.	✓	✓

✓= yes; X = no or unclear.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Laoire and Murtagh, 2017[15]</td></tr>
<tr><td>Based on one study of intravenous lidocaine for critical limb ischemia, the results are promising.
<table>
<tr><td>Group</td><td>Visual analogue scale score at baseline</td><td>Visual analogue scale score at 15 minutes post infusion</td><td>Visual analogue scale score at 30 minutes post infusion</td></tr>
<tr><td>Lidocaine</td><td>7.50</td><td>5.75 ± 1.77</td><td>4.25 ± 1.48</td></tr>
<tr><td>Morphine</td><td>7.65</td><td>7.00 ± 1.83</td><td>6.50 ± 1.73</td></tr>
<tr><td>Differences between two groups, reported as mean and 95% CI</td><td>0.15</td><td>1.25,
95% CI 0.095 to 2.405</td><td>2.25,
95% CI 1.218 to 3.282</td></tr>
</table>
A lower visual analogue scale score indicates a decrease in pain. The review authors reported that there were no side effects, adverse effects or serious complications based on follow-up for 30 minutes. No other outcomes were reported in the review. It is not reported if the VAS scores were reported with a standard error or a standard deviation.</td><td>"… a number of novel approaches to manage pain in this cohort have shown positive results and require further investigation. These include the use of intravenous lidocaine for short-term relief of ischemic pain in critical limb ischemia …There are a number of research possibilities emerging following this review. Intravenous lidocaine use for ischemic pain looks promising; however, further research needs to assess its use and safety over a longer duration." (p. 10)</td></tr>
<tr><td colspan="2">van der Wal et al., 2016[16]</td></tr>
<tr><td>There were 11 included studies addressing intravenous lidocaine as a clinical (human) intervention to relieve chronic pain in this review.

Systematic review: Intravenous lidocaine led to decreased pain compared to placebo but comparable to other treatments. Over 30% of patients receiving intravenous lidocaine had minor side effects compared to 12% of placebo.

Results from randomized controlled crossovers trials[a]
<table>
<tr><th>Study</th><th>Intravenous lidocaine dose(s) versus comparator</th><th>Duration of follow-up[b]</th><th>Outcomes favouring lidocaine; Outcomes not favouring lidocaine</th><th>Adverse effects</th></tr>
<tr><td>1</td><td>5 mg/kg in 30 minutes versus saline</td><td>NR</td><td>Favouring lidocaine: Spontaneous pain and brush evoked dysesthesia in all patients.
Not favouring lidocaine: Cold allodynia, pinprick hyperalgesia, pain evoked by repetitive pinprick</td><td>NR</td></tr>
</table></td><td>"Clinical studies demonstrate lidocaine to have a beneficial effect in abdominal surgery and in some neuropathic pain syndromes. We recommend more trials to be performed, with larger study size and impeccable methodology to determine the effect of iv lidocaine on the neuroinflammatory response in acute and chronic pain. More research has to be done assessing optimal dosing regimen of [intravenous] lidocaine" (p. 671)</td></tr>
</table>

Table 6: Summary of Findings Included Systematic Reviews

Main Study Findings					Authors' Conclusion
2[c]	5 mg/kg in 4 hours versus NS1209,[d] 322 milligrams intravenous	NR	**Favouring lidocaine:** none. **Not favouring lidocaine**: None	NR	
2[c]	5 mg/kg in 4 hours versus saline	NR	**Favouring lidocaine:** Brush evoked pain and cold allodynia. **Not favouring lidocaine:** Spontaneous pain	NR	
3	5 mg/kg in 30 min versus saline.	NR	**Favouring lidocaine**: Spontaneous pain (minimal effect), pain evoked by pinprick stimuli **Not favouring lidocaine:** Brush evoked pain, cold allodynia.	NR	
4	1, 3, 5 mg/kg in 6 hours versus saline	4 hours after stop infusion	**Favouring lidocaine:** 5 mg/kg/h reduces amount of pain lasting for four hours. Effect of other doses not reported. **Not favouring lidocaine:** NR	Mild adverse events.	
5	5 mg/kg in 4 hours, 7.5 mg/kg versus saline	28 days	**Favouring lidocaine:** Pain is reduced for 14 days, up to 28 days. Dosage of 7.5 mg/kg gives a slightly longer response. Effect of other doses not reported. **Not favouring lidocaine:** NR	NR	
6	1 mg/kg/hour for 1 hour; 5 mg/kg/hour for 1 hour versus placebo	NR	**Favouring lidocaine**: Reduction of pain in all groups, no differences between groups. **Not favouring lidocaine:** NR	NR	

Table 6: Summary of Findings Included Systematic Reviews

Main Study Findings	Authors' Conclusion
Retrospective one-arm studies: Four additional single-arm studies demonstrated that lidocaine was effective in reducing pain at baseline, but these studies are clearly limited by the lack of a control group.	

CI = confidence interval; mg/kg = milligrams per kilogram of body weight; NR = not reported.

[a] All data from van der Wal et al.[16] (p. 668). No numerical data were available. Studies did not report all dose comparisons. The review had no risk of bias assessment of individual studies. It is not known if individual studies had protocols and if other outcomes were measured and not reported in individual studies.

[b] Duration reported may be an indicator of duration of effectiveness, not necessarily full follow-up time.

[c] Study #2 included 2 comparisons, which are reported on separate lines in this table.

[d] NS1209 is a pain treatment, not otherwise defined.

Table 7: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Fitzcharles et al., 2012[17,19]	
"*Physicians should be aware that only pregabalin and duloxetine have Health Canada approval for management of fibromyalgia symptoms and all other pharmacologic treatments constitute 'off label use*'" (p. 123)	• Treatment Classification: Level 5, Opinion. • Grade of Recommendation: Consensus: Opinion supported by entire Canadian Fibromyalgia Guidelines Committee[19]
Mailis and Taenzer, 2012[18]	
"In patients with neuropathic pain, who have not derived sufficient benefit from pharmacological treatment, clinicians may consider a trial of intravenous lidocaine at doses of 5 mg/kg to 7.5 mg/kg body weight for pain relief lasting from a few hours to four weeks." (p. 153)	Following the US Preventive Services Task Force grading system (quotations from Mailis and Taenzer[18]): • Evidence quality: Good; *"Results must be consistent; the studies are well designed; the populations are representative*." (p. 152) • Certainty: Moderate; "*While the available evidence is sufficient to determine the effects on health outcomes; confidence in the estimate is constrained by the number, size or quality of studies, inconsistency of findings, limited generalizability or lack of coherence in chain of evidence. Further studies may change the conclusion*." (p. 152) • Strength of recommendation: Grade B "*High certainty with moderate effect or moderate certainty with moderate to substantial effect*" (p. 152)