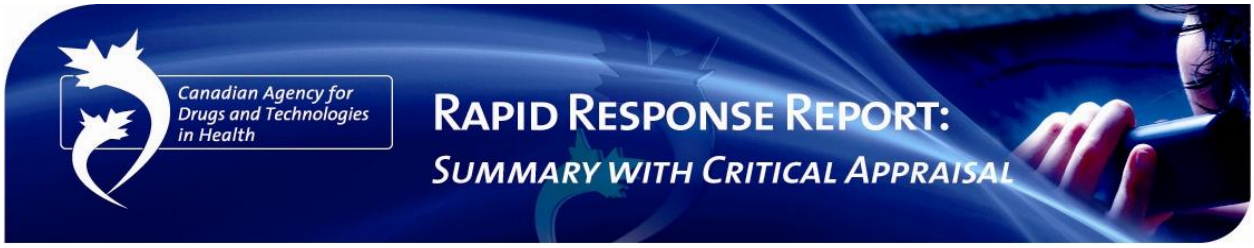

TITLE: Opioid Management Practices for the Prevention of Drug Diversion and Misuse: A Review of the Clinical Evidence and Guidelines

DATE: 13 April 2012

CONTEXT AND POLICY ISSUES

Opioids are indicated as part of a comprehensive plan for the management of chronic pain in carefully selected and monitored patients.[1] A marked increase in the misuse, abuse, and diversion of prescription opioids, however, has become a societal and public health concern and has led to increased healthcare costs and alterations in treatment plans.[1] Non-medical use of prescription opioids is a public health concern because it has been linked to serious personal health consequences, including addiction, fatal opioid overdose, injection drug use and poly drug use.[2] Opioid diversion signifies any instance where drugs are re-routed from their lawful purpose at any point in the pharmaceutical manufacturing and distribution process.[3] For example, opioids can be diverted in the preclinical stages through theft at plants, in transit or at pharmacies. Opioids can also be diverted during the post-clinical phase by sharing, selling and misusing of prescribed medications or by stealing medications.[3] Opioid misuse can be defined as the use of opioids for a medical purpose, other than as directed or indicated, whether or not intentional and regardless of harm.[1] Substance abuse can be defined as the use of any substance when such use is unlawful, or when such use is detrimental to the user or others.[1] The distinctions between these terms are often blurred and within the literature there has been no consensus around the definitions of opioid diversion, opioid misuse and substance abuse.

In Canada, the prescribing of opioids has increased dramatically in recent years.[4] For example, oxycodone prescriptions among Ontario Drug Benefit recipients rose from 1991 to 2007, from 23 prescriptions per 1000 individuals per year to 197 prescriptions per 1000 individuals per year.[4] These increases have been accompanied by increases in opioid-related harms such as addiction and overdose.[4] Of the 1095 people who died of opioid-related overdose in Ontario, during 1991 to 2007, 56% had been given opioid prescriptions within four weeks before death.[5]

The purpose of this report is to review the clinical evidence regarding opioid management practices to reduce drug diversion and misuse; examine the evidence-based guidelines for opioid management practices to reduce opioid diversion and misuse; and examine the clinical evidence regarding opioid use or prescription patterns for the prediction of substance abuse.

RESEARCH QUESTIONS

1. What is the clinical evidence regarding opioid management practices to reduce drug diversion and misuse?

2. What are the evidence based guidelines for opioid management practices to reduce opioid diversion and misuse?

3. What is the clinical evidence regarding opioid use or prescription patterns for prediction of substance abuse?

KEY MESSAGE

There is no one set of policies or practices that have been consistently associated with a reduction in opioid diversion and misuse. There is some evidence to suggest increased monitoring of patients and governmental prescription monitoring programs could have some impact on reducing opioid diversion and misuse. Evidence-based guidelines suggest frequently monitoring and assessing patients, using a diverse battery of techniques to prevent opioid diversion and misuse. There may be distinct patterns of opioid use associated with substance abuse and guideline recommended opioid prescription practices may reduce substance abuse.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Ovid Medline, PubMed, The Cochrane Library (2012, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI Health Devices Gold, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and March 16, 2012.

Selection Criteria and Methods

One reviewer screened citations retrieved from the literature search based on titles and abstracts, identified potentially relevant articles for full-text review and selected relevant articles regarding opioid management practices to prevent drug diversion and misuse and opioid use or prescription patterns as predictors of substance abuse. Details of the selection criteria are presented in Table 1.

Table 1: Selection Criteria

Population	Patients receiving opioids
Intervention	Q1, Q2 – opioid management practices (including coverage, dispensing and other management) Q3 – Difference in drug use patterns (e.g. doubling/tripling of narcotic dose in <2 months with no other concomitant therapy)

Comparator	No comparator specified
Outcomes	Opioid diversion Opioid misuse Unintended consequences such as increased use of other drugs (e.g. if narcotics are more restricted, does use/abuse of benzodiazepines increase) Guidelines on opioid management
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and evidence based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to 2007, already reported in one or more of the included systematic reviews, health technology assessments or meta-analyses, or were narrative or editorial reviews.

Critical Appraisal of Individual Studies

Critical appraisal of the included studies was performed based on study design. RCTs and non-randomized studies were assessed using the Downs and Black instrument.[6] Evidence-Based Guidelines were assessed using the Appraisal of Guidelines for Research and Evaluation II(AGREE II).[7]

SUMMARY OF EVIDENCE:

Quantity of Research Available

The literature search yielded 419 citations. Upon screening titles and abstracts, 29 potentially relevant articles were retrieved for full-text review. An additional six potentially relevant articles were identified through grey literature and hand searching. Of these 35 potentially relevant reports, 24 did not satisfy the inclusion criteria and were excluded. Of the 11 relevant articles included, one was a randomized controlled trial (RCT),[8] five were non randomized studies,[2,9-12] and five were evidence-based guidelines,[13-17] two of which were one guideline reported in two parts in two separate publications.[14,15] No relevant health technology assessments or systematic reviews were identified. Details of the study selection process are outlined in Appendix 1.

Summary of Study Characteristics

Characteristics of the included studies are summarized below and details are provided in Appendix 2.

Study Design
There were six studies and four evidence-based guidelines. The six included studies were composed of one RCT,[8] three retrospective cohort studies,[9-11] and two cross-sectional studies [2,12] that were all conducted in the United States of America (USA). Of the four guidelines included in this review, three were American[13,16,17] and one was Canadian.[14,15]

Populations

Of the six included studies, five studies were on adults receiving opioids (for treatment or recreational use)[2,8-10,12] and one study compared patients receiving opioids with non-opioid users.[11]

Of the four guidelines, three guidelines were on opioid use in adult patients with chronic non-cancer pain[13-16] and one guideline addressed the management of chronic pain in patients ages 16 and above.[17]

Interventions

The one RCT compared the effectiveness of different treatment approaches for prescribing opioids based on dose.[8]The three retrospective cohort studies examined the effect of opioid management practices, including prescription monitoring.[9-11] The two cross-sectional studies examined differences in opioid use.[2,12]

All four guidelines provided recommendations on the use of opioids, including screening, assessing and monitoring recommendations to assist in identifying patients who may benefit from opioid treatment.

Outcomes

The main outcomes in the six included studies varied considerably. The main study outcomes in the RCT were pain, pain relief, and medication discontinuations due to non-compliance.[8] Main study outcomes in the three retrospective cohort studies included mortality, prescription opioids users (schedule II, III, and IV),[9] opioid treatment admissions and intentional exposures,[12] reassessment of pain, assessment of pain related function, assessment of opioid adverse effects, assessment of pain treatment adherence, assessment of active or past alcohol or drug use, urine testing, and completion of an opioid treatment agreement.[10] The main study outcomes of the two cross-sectional studies included subgroups of substance abusers, risk of overdose, and risk of blood-borne viral infection;[2] opioid misuse, problem opioid misuse, any non-opioid illicit drug use, non-opioid problem drug use, problem alcohol use.[11]

All the guidelines developed recommendations for opioid management.[13-15,17]

Summary of Critical Appraisal

The included RCT had clearly described methods including a description of the inclusion and exclusion criteria, and patient follow-up and discontinuations. However, there was no information provided on blinding of study personnel or patients. In addition, data and results were not provided for all of the outcomes described in the methods section, most notably for the purposes of this review, scores on the Addiction Behaviours Checklist (ABC).

For the non-randomized studies, a list of potential confounding variables was not provided in four studies,[2,9,10,12] adverse events were incompletely reported or not reported in six studies,[2,8-12] and for the two studies where the study sample was recruited from a source population, no data was provided to determine if the sample was reflective of the original source populations.[2,10] In two studies analyses were adjusted for covariates.[2,11] Two studies examined how the implementation of guidelines affect opioid dosing and opioid misuse.[9,10]

For the guidelines, objectives were clearly specified, clinical questions and target populations and audiences were clearly defined. All guidelines were developed by multidisciplinary panels or committees, which appear reflective of the health professionals managing patients treated with opioids. In addition, all the included guidelines provided a transparent assessment structure for grading the available evidence. However, none of the guidelines considered input from patients. Criteria for selecting evidence in all cases were clearly described and the strengths and limitations of the evidence were clearly described. One guideline was vague, in terms of the definition of chronic pain and its recommendations for opioid management.[13]

Details of the critical appraisal are presented in Appendix 3.

Summary of Findings

The findings are summarized below and details are provided in Appendices 4 and 5.

Three studies addressed the issue of opioid misuse.[10-12] A retrospective cohort study[12] conducted by Reifler et al. (2011) examined the relationship between statewide prescription monitoring programs (PMPs) and opioid misuse over time, using two drug abuse surveillance data sources. States with PMPs experienced significantly smaller increases (0.2%) in intentional exposures (a surrogate for misuse and abuse) compared to those without a PMP in place (1.9%) (p= 0.036).[12] This study suggested that in USA one approach to reduce opioid misuse was to have statewide PMPs.[12]

Another retrospective cohort study[10] conducted by Krebs et al. (2011) attempted to characterize long-term opioid prescribing and monitoring practices in primary care clinics. Findings suggest patients with indicators of potential opioid misuse had more primary care clinic visits during the 6 month study period than those without misuse indicators (2.8% vs. 2.2%, p= 0.014). Indicators of potential opioid misuse include three categories of activities: serious aberrant behaviours, minor aberrant behaviours, and substance abuse. Serious aberrant behaviours were defined as opioid diversion, buying opioids from illicit sources and deliberately obtaining opioids from multiple prescribers. Minor aberrant behaviours were defined as reporting opioids lost or stolen, requesting early refills (two times or more), aggressive demanding of more opioids, and missing multiple primary care appointments. Substance abuse was defined as documented active alcohol or drug abuse, trauma or arrest related to intoxication or urine drug test that was positive for an illicit drug. In addition, compared to patients without misuse indicators, patients with potential misuse indicators had significantly more documented opioid-monitoring practices in their records (2.4% vs. 1.3%, $p < 0.001$). Opioid monitoring practices included: reassessment of pain, assessment of pain-related function, assessment of opioid adverse effects, assessment of pain treatment adherence, assessment of active or past alcohol or drug use, urine drug testing and completion of an opioid treatment agreement. It is unclear whether these additional monitoring practices were initiated before patients could be classified as opioids misusers or whether the presence of potential misuse indicators qualified a patient as an opioid misuser.[12]

Data from a cross-sectional survey[11] of adults was used to determine whether individuals who use prescribed opioids for chronic noncancer pain have higher rates of opioid misuse, or problem opioid misuse when compared to non-opioid users. Use of prescribed opioids was defined as taking prescribed medications at least several times a week for a month or more in the past 12 months. Participants who did not meet the criteria for opioid use were categorized as non-opioid users. Opioid misuse was defined as patients who identified the use of psychoactive substances on their own, in particular analgesics or other prescription painkillers

and this did not include drugs such as aspirin and Tylenol without codeine. The definition for problem opioid misuse included the criteria of tolerance and/or psychological problems due to drug use in addition to the criteria included in the definition of opioid misuse. The odds of any opioid misuse were more than five times greater among opioid users when compared to non-opioid users, odds ratio (OR)= 5.48 [95% confidence interval (CI)= 3.97 to 7.56] in the unadjusted model. After controlling or adjusting for the covariates of mental health disorders, physical health, level of pain-related interference, chronic physical health conditions, and sociodemographic variables, the odds of opioid misuse was about three times greater for opioid users when compared to non-opioid users, OR=3.07 (95% CI= 2.05 to 4.60). The odds of problem opioid misuse was nearly 15 times greater for opioid users when compared to non-opioid users, OR= 14.76 (95% CI = 7.11 to 30.64) in the unadjusted model. After controlling or adjusting for the same covariates described in the any opioid use analysis, the odds of problem opioid misuse was approximately six times greater for opioid users when compared to non-opioid users, OR =6.11 (95% CI= 3.02 to 12.36).[11]

Four guidelines concerning opioid management practices were identified.[14-17] Each offered multiple recommendations and insights into methods to reduce opioid diversion and misuse. All the guidelines recommended assessing and monitoring patients. Specifics of the strategies used varied.

Five of the 25 recommendations in the one included Canadian Guideline were directed towards opioid misuse and diversion.[14,15] These recommendations were directed at selecting patients; dose initiation and titration; monitoring; treating opioid addiction; reducing prescription fraud, disagreements with opioid prescription or unacceptable behaviour; and policy development for acute or urgent health care facilities.[14,15]

The Institute for Clinical Systems Improvement (ICSI) guidelines offered general recommendations for opioid management, which could be related to deterring opioid misuse and diversion, including monitoring and maintaining opioid agreements, developing a process for scheduling follow-up visit and identifying assessment tools that examine multiple dimensions that meet the needs of healthcare providers and patients.
The American Pain Society (APS), in partnership with the American Academy of Pain Medicine (AAPM) developed guidelines about managing chronic opioid therapy (COT) for chronic non-cancer pain (CNCP) for clinicians treating adults with CNCP.[16] Their 25 recommendations covered 14 categories of pain management. Five of the 25 recommendations were relevant for the reduction of opioid diversion and misuse. The recommendations included instructions on the steps to initiate before COT, such as an assessment of risk of substance abuse, misuse or addiction; periodic reassessment of patients on COT and suggestions on areas to monitor; recommendations for monitoring patients who have engaged in aberrant drug-related behaviours; recommendations for monitoring patients on COT who are not at high risk and not known to have engaged in aberrant drug-related behaviours; recommendation of stringent monitoring for patients with history of engaging in aberrant behaviour, which may be predictors of potential problems when taking opioids.[16]

The American Society of the Intervention of Pain Physicians' (ASIPP) Guidelines mentioned a ten-step process for long-term opioid use in chronic pain.[13] This was considered by the authors as a weak recommendation based on high-quality evidence because the benefits were closely balanced with risks and burden. The methodological quality of the supporting evidence was based on RCTs without important limitations or overwhelming evidence from observational

studies. A weak recommendation, implied that the best action may differ depending on circumstances, patients or societal values.[13]
The three studies addressing opioid use and prescription patterns as predictor of substance abuse, included one RCT,[8] one retrospective cohort study[9] and one cross-sectional study.[2]

Naliboff et al.(2011)[8] examined the effectiveness of a stable dose approach for prescribing opioids (morphine equivalents) compared to an escalating dose approach. It was hypothesized there would be no significant differences between groups regarding substance abuse behaviours. Substance misuse or noncompliance discontinuations due to alcohol or illicit substance abuse accounted for 10% of discontinuations. Overall 22 patients (33%) in the stable dose group and 16 patients (26%) in the escalating dose group dropped out due to opioid medication or clinic non-compliance, the difference was non-significant.

Green et al. (2011)[2] attempted to derive and describe types of prescription opioid use, using a cross-sectional sample of adults (N= 26,314) in treatment for substance abuse or dependence using latent class analysis. A latent class analysis approach assumes that the study population represents not one homogenous group of prescription opioid users but a mixture of several distinct subgroups of medical and non-medical prescription opioid users. The subgroups are latent, that is they are not directly observable but they can be inferred based on similarities in individuals' responses to questions about their health behaviours and non-medical prescription opioid use. Employing such an analysis, people are empirically divided into groups rather than categorized a priori or by study design. Findings from the analysis indicated that a four class model generated the most clinically interpretable and relevant groups. The four groups were: Class 1 (use as prescribed) (number of patients [n] = 4973, 18.9% of the total population), Class 2 (prescribed misusers) (n= 7079, 26.9%), Class 3 (medically healthy abusers)(n=9420, 35.8%, and Class 4 (Illicit users) (n= 4842, 18.4%). Among these classes, there was the potential for unintended negative consequences for patients in class 2, 3, or 4 as they have a high risk for a potential overdose. In addition, patients in class 3 have an elevated risk of blood-borne viral infections [hepatitis B, hepatitis C, and human immunodeficiency virus (HIV)] and patients in class 4 have a high risk of blood-borne viral infections.

Franklin et al. (2011)[9] examined if the dissemination of the Washington (WA) State Agency Medical Director's Group (AMDG) Guidelines in April 2007, may have been associated with changes in trends in opioid dosing and mortality due to overdose in WA workers' compensation population. The number of opioid related deaths in WA workers' compensation population continued to rise in 2009 and dropped dramatically in 2010 (no data provided). The number of prescriptions for schedule II opioids peaked around 2006 and plateaued up to 2008 and this was followed by sharp decline in 2009 and 2010.The number of prescriptions for schedule III opioids declined through 2008, then declined more sharply in 2009 and 2010. In addition, the number of opioid related deaths continued to rise until 2009, followed by a dramatic drop in 2010.

Limitations

It was unclear in the one included RCT whether study personnel and participants were blinded to treatment assignment. With the lack of clear blinding criteria in the study, it is possible the study could be subject to experimenter's bias. For the non-randomized studies, the majority of studies were based on self-reported data which may be subject to recall bias and social desirability bias. In addition, in the non-randomized studies the definition of opioid users was not provided or no rationale was provided for the operational definitions used. Two of the five non-

randomized studies were based on cross-sectional data. These data sources are limited because one is unable to determine the temporal relationship between opioid use and the outcomes of interest (e.g. substance abuse). Furthermore, the included RCT and non-randomized studies were not conducted in Canada hence the findings may not be generalizable to the Canadian setting. The included guidelines did not consider any patient input. In addition, there was little evidence provided to justify that the recommendations would have a tangible benefit on opioid misuse or diversion (e.g. previous studies that implemented the measures and observed significant reductions in opioid misuse or diversions were not reported).

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

The clinical evidence regarding opioid management practices to reduce drug diversion and misuse was generally of low-quality. The available evidence suggested prescription monitoring programs may be an effective approach to reduce drug diversion and misuse in the form of a reduction in intentional exposures. However, it was unclear the direct impact these programs may have on drug diversion and misuse. The available literature also suggested increased monitoring for patients at risk of drug diversion and misuse. However, it was unclear whether the increased monitoring had a direct impact on reducing drug diversion and misuse. In addition, it was possible that some of the issues associated with opioid misuse were mediated by the presence of mental illness. However, high-quality evidence is needed before definitive conclusions can be made on whether there are any relationships among opioid use, mental illness, and opioid misuse and diversion.

Generally, guidelines on opioid use suggested similar strategies to reduce opioid diversion and misuse. These strategies included detailed multidimensional assessments before selecting patients for treatment with opioids, ongoing monitoring with multidimensional assessments, scheduled follow-up, policy development, low dose initiation and gradual dose titration.

There was limited quantity of low quality evidence regarding opioid use or prescription patterns as a predictor for substance abuse and were based on widely varied study designs. The choice of stable dose or dose escalation did not appear to be a predictor of substance abuse. It was possible that substance abusers had characteristics that differed from those of individuals that used their medications as prescribed. In one study implementation of a guideline appeared to reduce prescriptions for opioids. However, high-quality evidence is required before definitive conclusions can be drawn as to whether patient characteristics, opioid use and prescription patterns could play a role in predicting the risk of substance abuse.

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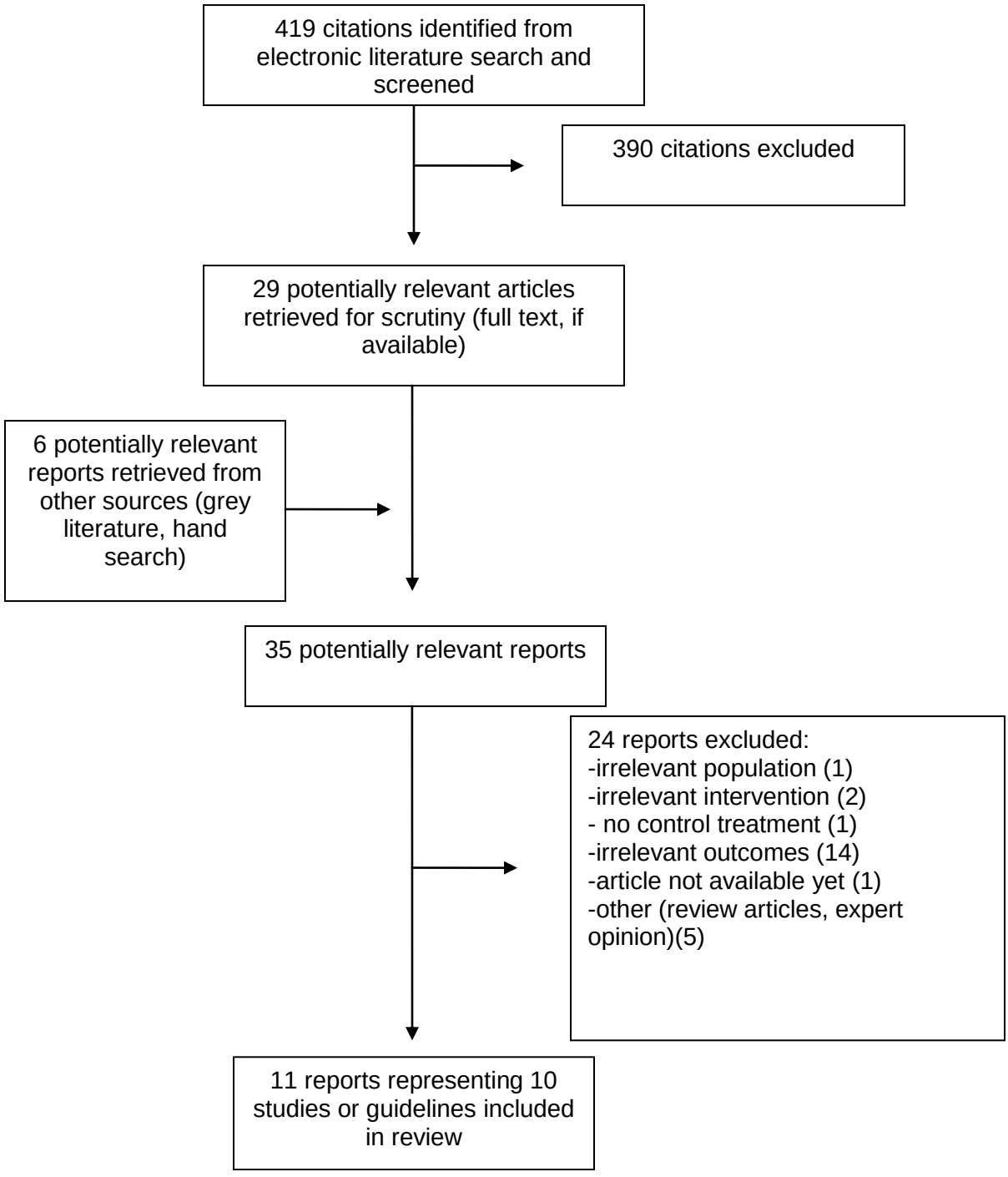
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Randomized and Non-randomized Studies

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Randomized controlled trial					
Naliboff et al. (2011),[8] USA	RCT, 12 month	Sequential adult referrals to a Chronic Pain Clinic (N= 140)	Stable dose or morphine equivalents	Escalating dose of morphine equivalents	Addiction Behaviours Checklist (ABC) pain, pain relief, medication discontinuations for non compliance
Non-randomized studies					
Franklin et al. (2012), [9] USA	Retrospective Cohort Study , from 2003 to 2010,	Prescription Opioids users from a workers compensation system In Washington State, sample size is not reported	Implementation of an opioid management guideline (guideline AMDG added in April 2007)	No comparator	mortality; number of prescription opioid users using schedule II, III and IV opioids;
Reifler et al. (2012) ,[12] USA	Retrospective cohort study, data on opioid treatment from first quarter of 2005 to third quarter of 2009, and Poison Center Data from first quarter of 2003 to third quarter of 2009	Prescription opioid users; sample size is not reported	Prescription Monitoring Programs, (in 33 out of 50 states)	Without Prescription Monitoring Programs, (in 17 out of 50 states)	Opioid Treatment Admissions Intentional exposures (a surrogate for misuse and abuse)
Green et al. (2011),[2] USA	Cross-sectional study November 2005 to December 2009	Prescription opioid users; N= 26,314	Drug use patterns	No comparator	Latent class analysis to determine the subgroups of substance abusers, risk of overdose, risk of blood-borne viral infection
Krebs et al. (2011), [10] USA	Retrospective Cohort Study May 1, 2006 to April 30, 2007	Patients who filled $\geq$ 6 prescriptions for opioids; N= 250	Documentation of opioid monitoring practices recommended in the 2003 VA/DoD Clinical Practice Guidelines	No comparator	presence or absence of: reassessment of pain, assessment of pain related function assessment of opioid adverse effects, assessment of pain treatment

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
					adherence, assessment of active or past alcohol or drug use, urine testing, and completion of an opioid treatment agreement
Edlund et al. (2007),[11] USA	Cross-sectional survey 1996 to 1997	Adult survey (Opioid users vs. non-opioid users) N= 9,279	Differences in prescribed opioid use	No comparators	Opioid misuse, problem opioid misuse, any non-opioid illicit drug use, non-opioid problem drug use, problem alcohol use
ABC=Addiction Behaviours Checklist; **AMDG=** Agency Medical Director's Group; **DoD**= Department of Defence; N = total sample size; **RCT=** randomized controlled trials; **VA=** Veterans' Affairs; **USA=** Untied States					

Appendix 3 : Summary of Critical Appraisal of Included Studies and Guidelines

First Author, Publication Year	Strengths	Limitations
Randomized Controlled Trial		
Naliboff et al. (2011)[8]	• Included a comparison of treatment strategies based on dose to investigate the impact on opioid misuse and abuse • Randomized	• No measures of adherence or compliance included • No information on blinding of any personnel or patients involved in the study • Adverse events not reported
Non-randomized Studies		
Franklin et al. (2012)[9]	• Large dataset • Long duration • Examined how implementation of a guideline impacted opioid dosing	• Descriptive statistics, • No inferential statistical analysis • Data not provided for some of the key outcomes • No list of potential cofounding variables • Adverse events reports incomplete
Reifler et al. (2012)[12]	• Large dataset • Statistical analysis methodology was appropriate and well described	• Self–reported data, which may be subject to recall and social desirability biases • Data may be subject to selection bias as analysis was limited to patients who received prescriptions for fentanyl, hydromorphone, methadone, morphine, and oxycodone • Variations in quality and coverage of PMPs were not included in the analysis • No list of potential cofounding variables • Adverse events not reported
Green et al. (2011)[2]	• Analysis adjusted for covariates • Included determination of possible predictors of substance abuse	• Cross-sectional data cannot determine the temporal relationship between opioid use and substance • Self-report data subject to recall and social desirability biases • No list of potential cofounding variables • Unclear if the study sample reflected the original source population • Adverse events not reported •
Krebs et al. (2011)[10]	• Examined how following a guideline recommended management approach affects opioid misuse	• Cross-sectional data • Small sample size • Chart review data is frequently incomplete • Unclear if the study sample reflected the original source population • Adverse events not reported
Edlund et al. (2007)[11]	• Present adjusted and unadjusted analysis	• Small proportion of opioid users within the large sample may limit the generalizability of these findings • Survey question were not designed for the purposes of examining opioid use in this study • No rationale provided for the operational definition of opioid user adopted in the study • Self-reported data subject to recall bias • Adverse events not reported
Evidence- Based Guidelines		
ICSI Guideline (2011)[17]	• Transparent assessment structure for grading the available evidence	• Little information on opioid management practices to reduce opioid diversion and

First Author, Publication Year	Strengths	Limitations
	• Provides multiple management algorithm for different types of pain • Guidelines were developed by multidisciplinary panels or committees, which appear reflective of the health professionals managing patients treated with opioids • Objectives were clearly specified, clinical questions and target populations and audiences were clearly defined	misuse • Guidance for physicians related to substance abuse is primarily based on outdated guidelines • Guideline does not provide specific recommendations • Unclear if patient input was considered
Canadian Guideline for Safe and Effective use of Opioids for CNCP (2010) [14,15]	• Comprehensive guideline: addressed multiple areas including drug diversion and misuse, • Transparent assessment structure for grading the available evidence • Provides direct guidance and advice for healthcare providers • Guidelines were developed by multidisciplinary panels or committees, which appear reflective of the health professionals managing patients treated with opioids • Objectives were clearly specified, clinical questions and target populations and audiences were clearly defined	• Vast majority of studies identified in the literature were non-randomized • Many of the studies lacked included for the literature review lacked important outcomes such as potential-long-term complications of opioid misuse • Unclear if patient input was considered
Chou et al.(APS and APPM Guidelines) (2009)[16]	• Includes guidance for special populations • Clearly identified and describes the quality of the evidence used to make this recommendation • Transparent assessment structure for grading the available evidence • Guidelines were developed by multidisciplinary panels or committees, which appear reflective of the health professionals managing patients treated with opioids • objectives were clearly specified, clinical questions and target populations and audiences were clearly defined	• Unclear whether the input of patients was sought during the development of this guideline
ASIPP Guidelines(2008) [13]	• Transparent assessment structure for grading the available evidence • Included reduction opioid abuse and diversion in the objectives • Guidelines were developed by multidisciplinary panels or committees, which appear reflective of the health professionals managing patients treated with opioids • Objectives were clearly specified, clinical questions and target populations and audiences were clearly defined	• Vague definition of chronic pain • No specific recommendations on opioid management • Unclear if patient input was considered
APS=American Pain Society; **ASIPP=** American Society of the Interventional Pain Physicians' Guidelines; **CNCP**=Chronic Non-Cancer Pain;		

APPENDIX 4: Summary of Main Study Findings and Author's Conclusions

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Randomized controlled trial		
Naliboff et al. (2011)[8]	• Substance misuse or noncompliance discontinuations due to alcohol or illicit substance abuse accounted for 10% of discontinuations from the study • Noncompliance with medications accounted for 15% of discontinuations from the study. • Overall 22 patients (33%) in the stable dose group and 16 patients (26%) in the escalating dose group dropped out due to opioid medication or clinic non-compliance, the difference was non-significant	Study confirms that even in carefully selected tertiary care patients, substance misuse is a significant problem
Non-randomized studies		
Franklin et al. (2012)[9]	• Number of opioid related deaths in WA workers' compensation population continued to rise until 2009 and then dropped dramatically in 2010 (no data provided) • Number of prescriptions for schedule II* opioids peaked around 2006 (66,544). It plateaued from 2006 to 2008(data not provided for 2007 and 2008). This was followed by a sharp decline in 2009 (54,484), which continued in 2010 (44,209) • Number of prescriptions for schedule III* opioids declined through 2008. It was 79,882 in 2008, then declined more sharply to 63,808 in 2009 and 52,499 in 2010	It is possible that additional prescription opioid-related deaths could be prevented by more intensive efforts to educate health care providers about opioids
Reifler et al. (2012) [12]	• States with PMPs experienced significantly smaller increases (0.2% per quarter) in intentional exposures (a surrogate for misuse and abuse) compared to those without a PMP in place (1.9% per quarter) (p= 0.036).The opioid treatment admissions increased on average 4.9% per quarter in states without a PMP vs 2.6% per quarter in states with a PMP (p= 0.058).	Findings from the two data sources support that PMPs are associated with mitigation of increasing opioid abuse and misuse over time in both the general population as well as within the population seeking treatment at Opioid Treatment programs
Green et al. (2011)[2]	A four class model defined four clinically interpretable and relevant groups, based on their patterns of item response Class 1 (use a prescribed) (n= 4,973 [18.9%]) Class 2 (prescribed misusers) (n= 7079[26.9]) Class 3 (medically healthy abusers) (n=9420)[35.8%]) Class 4 (Illicit users) (n=4842) [18.4]) Cross class comparisons and pairwise comparison were all statistically significant (p<.05) Class 1 use as prescribed were characterized by a general lack of problematic drug use- including non-medical prescription opioid use Class 2 exhibited similar medical problems to those using a prescribed, histories of current and past drug abuse	This study detected multiple distinct profiles of prescription opioid users, suggesting a range of typologies rather than a simple dichotomy of those who do or do not report non-medical use of prescription opioids. For most patterns, non-medical prescription opioid use did not occur in isolation of abuse of other substances. The prominence of comorbid psychiatric and medical problems suggest the need for better integration of and access to mental health, primary care and substance abuse treatments

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	Class 2 had significantly higher rates of lifetime depression, lifetime anxiety and currently prescribed psychiatric medications than any other class Class 3 reported using alcohol to intoxication most often, Class 3 and four reported current illicit drug use and recent initiation of non-medical use of prescription opioids, heroin, and injection drug use. Unintended consequences of classification in classes 2, 3, and 4 were patients in these classifications were at high overall overdose risk potential Class 3 had elevated risk of blood-borne viral infections† Class 4 had a high risk of blood-borne viral infection potential risk	
Krebs et al. (2011) [10]	• 53% of patients had a medical record indicator of potential opioid misuse present at 12 months • Patients with indicators of potential opioids misuse had more primary care clinic visits during the 6 month study window than those without misuse indicators (2.8% vs. 2.2%, p= 0.014) • Those with potential misuse indicators had significantly more documented opioid-monitoring practices in their records (2.4% vs. 1.3%, p< 0.0001), alcohol and drugs (26% vs. 8%, p= 0.004), opioid treatment agreement (18% vs. 8%, p= 0.047) and urine testing (35% vs. 5%, p = 0.001)	Guideline recommended opioid monitoring practices were infrequently documented in primary care
Edlund et al. (2007)[11]	Problem opioid misuse: Unadjusted OR= 5.48 (95% CI= 3.97 to 7.56, p< 0.0001) Adjusted OR= 3.07 (95% CI= 2.05 to 4.60, p< 0.001) in the fully adjusted model Any opioid misuse: Unadjusted OR= 14.76 (95% CI= 7.11to 30.64) Adjusted OR= 6.11 (95% CI= 3.02 to 12.36)	Users of opioids had higher rates of opioid and non opioid abuse problems compared with nonusers of opioids, but these rates appear to be partially affected by factors such as common mental health disorders, physical health, pain and sociodemographic status. Clinicians need to diagnose and treat these substance abuse problems in the context of mental disorders.

CI= confidence interval, n= subgroup population size; OR= Odds Ratio, PMP= Prescription Management Programs; WA= Washington;
* Schedule II and Schedule III are classifications on the Controlled Substances Act in the USA
† blood borne viral infections were hepatitis C, hepatitis B, and human immunodeficiency virus (HIV)

APPENDIX 5: Summary of Guidelines and Recommendations on Opioid Management

Guideline Society or Institute, Year	Recommendations
ICSI Guidelines for the Assessment and Management of Chronic Pain (2011) [17]	Establish a policy for monitoring and maintaining opioid agreements Develop a process involving physicians and other care workers for scheduling follow-up patient visits to deter drug seeking behaviours; such as support personnel calling patients to schedule follow-up appointments with a dedicated chronic pain physician Identify multidimensional pain assessment tools, which include functional assessment, psychological assessment, and opioid assessment tools, that meet the needs of the care providers and are appropriate for the patients
Canadian Guideline for Safe and Effective use of Opioids for CNCP (2010) [14,15]	When initiating a trial of opioid therapy for patients at higher risk for misuse, prescribe only for well-defined somatic or neuropathic pain conditions (Grade A), start with lower doses and titrate in small-dose increments (Grade B), and monitor closely for signs of aberrant drug-related behaviours (Grade C) For patients with CNCP who are addicted to opioids, 3 treatment options should be considered: methadone or buprenorphine treatment (Grade A), structured opioid therapy (Grade B), or abstinence-based treatment (Grade C). Consultation or shared care, where available, can assist in selecting the best treatment option (Grade C). To reduce prescription fraud, physicians should take precautions when issuing prescriptions and work collaboratively with pharmacists (Grade C). Be prepared with an approach for dealing with patients who disagree with their opioid prescription or exhibit unacceptable behaviour (Grade C). Acute or urgent health care facilities should develop policies to provide guidance on prescribing opioids for chronic pain to avoid contributing to opioid misuse or diversion (Grade C).
Chou et al.(APS and AAPM, USA Guidelines) (2009)[16]	Before initiating COT, clinicians should obtain a history, conduct physical examination and appropriate testing, including an assessment of risk of substance abuse, misuse, or addiction (strong recommendation, low-quality evidence) Clinicians should reassess patients on COT periodically and as warranted by changing circumstances. Monitoring should include documentation of pain intensity and level of functioning, assessments of progress toward achieving therapeutic goals, presence of adverse events and adherence to prescribed therapies (strong recommendation, low quality evidence) In patients on COT who are at high risk or who have engaged in aberrant drug-related behaviours, clinicians should periodically obtain urine drug screens or other information to confirm adherence to COT plan of care (strong recommendation, low quality evidence) In patients on COT not at high risk and not known to have engaged in aberrant drug-related behaviours, clinicians should consider periodically obtaining urine drug screens or other information to confirm adherence to the COT plan of care (weak recommendation, low-quality evidence) Clinicians may consider COT for patients with CNCP and history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviours only if they are able to implement more frequent and stringent monitoring parameters (strong recommendation, low-quality evidence)

Guideline Society or Institute, Year	Recommendations
ASIPP Guidelines, USA (2008)[13]	Overall the recommendation is a 2A- weak recommendation, high-quality evidence: with benefits closely balanced with risk and burden; derived from RCTs without important limitations or overwhelming evidence from observational studies, with the implication that with a weak recommendation, best action may differ depending on circumstances or patients' societal values. Recommended 10 step treatment algorithm is outlined on p. 547 in Table 19 I. Comprehensive initial evaluation II. Establish diagnosis III. Establish medical necessity (lack of progress or as supplementary therapy) IV. Assess risk-benefit ratio V. Establish treatment goals VI. Obtain informed consent and agreement VII. Initial dose adjustment phase (up to 8 to 12 weeks) VIII. Stable phase IX. Adherence monitoring X. Outcomes

AAPM= American Academy of Pain Medicine;**; APS=**American Pain Society; **ASIPP**= American Society of the Interventional Pain Physicians' Guidelines; **CNCP=** Chronic Non-Cancer Pain; **ICSI**=Institute for Clinical Systems Improvement

- For a description of the evidence grading for the guidelines please see Appendix 6

APPENDIX 6: Grading of Recommendations and Levels of Evidence

Guideline Society or Institute, Year	Levels of Recommendation	Level of Evidence
ICSI Guidelines for the Assessment and Management of Chronic Pain (2011)[17]	**"Grade I:** The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, flaws in research design. Studies with negative results have sufficiently large sample to have adequate statistical power. **Grade II**: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most. **Grade III:** The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from limited number of studies of weak design for answering the question addressed. **Grade Not Assignable:** There is not evidence available that directly supports or refutes the conclusion." (p84)[17]	Adapted Grading of Recommendations Assessment, Development and Education (GRADE) System- ICSI GRADE System
Canadian Guideline for Safe and Effective Use of Opioids for CNCP (2010) [14,15]	**"Grade A:** Recommendations are supported by evidence from RCTs. **Grade B:** Recommendations are supported by- evidence from controlled trials without randomization; evidence from cohort or case-control analytic studies, preferably from more than once center or research group; OR evidence from comparisons between times or places with or without the intervention, dramatic results in uncontrolled experiments could be included here.	

Guideline Society or Institute, Year	Levels of Recommendation	Level of Evidence
	Grade C: Recommendations are supported by consensus opinion of the National Advisory Panel." (Part A, p19)[14]	
Chou et al. (APS and AAPM Guidelines) (2009)[16]	Generally, a strong recommendation is based on the panel' assessment that potential benefits of the following the recommendation clearly outweigh potential harms and burdens. Given the available evidence, most clinicians and patients would choose to follow a strong recommendation A weak rating is based on more closely balanced benefits to harms or burdens, or weaker evidence.	GRADE For grading the quality of a body of evidence that supports a recommendation, we considered the type, number, size, and quantity of studies; strength of associations or effects; and consistency of results among studies
ASIPP Guidelines (2008)[13]	"1A- strong recommendation, high-quality evidence 1B- strong recommendation, moderate high quality evidence 1C- strong recommendation, low-quality or very low-quality evidence 2A- weak recommendation, high-quality evidence 2B- weak recommendation, moderate-quality evidence 2C- weak recommendation, low-quality or very low quality evidence" (Table 2, p59)[13]	Adapted from AHRQ "I: Evidence obtained from at least on properly RCT II-1: Evidence obtained from well-designed controlled trials without randomization II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group II-3: Evidence obtained from multiple time series with or without intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence III- Opinions of respected authorities, based on clinical experience descriptive studies and case reports or reports of expert committees" (Table 1, p58)[13]
AAPM= American Academy of Pain Medicine; **AHRQ**= Agency for Healthcare Research and Quality; **APS=**American Pain Society; **ASIPP=** American Society of the Interventional Pain Physicians' Guidelines; **ICSI=**Institute for Clinical Systems Improvement; **RCTs=** randomized controlled trials		