TITLE: Suboxone Versus Methadone for the Detoxification of Patients Addicted to Prescription Opioids: A Review of Comparative Clinical Effectiveness, Safety, and Guidelines

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CONTEXT AND POLICY ISSUES

Opioid addiction is a serious global public health problem that can result in premature disability and death.[1,2] The mortality rate of opioid-dependent persons is approximately thirteen times higher than that of the general population.[2] Canada's rate of prescription opioid use increased by 203% between 2000 and 2010, increasing the risk of opioid addiction and abuse.[3,4] The prevalence of opioid misuse in primary care settings is difficult to estimate due to patient under-reporting.[4] A three-year national longitudinal study conducted in the United States found that young adults were at increased risk of nonmedical opioid use, which increases the risk of future substance use disorders.[5]

Opioid addiction can be treated with pharmacologically active opioids that help relieve opiate withdrawal symptoms.[1] The treatment process involves stabilizing the patient through substitution treatments that minimize the dependence of drug use on mental state, detoxification to minimize withdrawal symptoms, and maintenance to prevent relapse.[6,7]

Methadone is a synthetic μ-opioid receptor agonist that reduces the euphoric effects of subsequent opioid use.[1] Methadone is administered orally in a liquid, tablet, or dispersible tablet formulation.[1] Suboxone was approved by Health Canada in 2007 for the treatment of opioid drug dependence in adults.[8] Suboxone is a fixed combination of buprenorphine (a partial μ-opioid receptor agonist) with naloxone (an opioid antagonist) in a 4:1 ratio.[9] Naloxone was added to buprenorphine in order to prevent the intravenous abuse of buprenorphine.[4] Suboxone is administered sublingually to minimize absorption of naloxone, which can precipitate opioid withdrawal when injected.[4]

The purpose of this review to examine the comparative clinical effectiveness of Suboxone versus methadone for the detoxification of patients addicted to prescription opioids. In addition, guidelines on the length of detoxification time using Suboxone in patients addicted to prescription opioids will be examined.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness and safety of Suboxone versus methadone when used as a tool for detoxification in patients addicted to prescription opioids?

2. What is the comparative clinical effectiveness of Suboxone versus methadone in achieving complete opioid abstinence in patients addicted to prescription opioids?

3. What is the comparative clinical effectiveness of Suboxone versus methadone for the relief of withdrawal symptoms and cravings in patients addicted to prescription opioids for less than 12 months?

4. What is the comparative clinical effectiveness of Suboxone versus methadone for the relief of withdrawal symptoms and cravings in patients addicted to prescription opioids who continue to frequently misuse central nervous system depressants?

5. What are the guidelines associated with the length of detoxification time using Suboxone in patients addicted to prescription opioids?

KEY FINDINGS

One RCT suggests that Suboxone and methadone were similar with regards to treatment retention and decreasing use of other opioids in patients with nonmalignant chronic pain and an addiction to a prescription opioid. One guideline suggests that a daily dose of Suboxone for 1 to 3 days should eliminate signs and symptoms of opioid withdrawal, suppress opioid cravings, and eliminate illicit opioid use in adults.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 1), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and January 9, 2014. Internet links were provided, where available.

Selection Criteria and Methods

One reviewer screened the titles and abstracts or the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients ≤ 30 years old who are addicted to prescription opioids
Intervention	Suboxone (buprenorphine/naloxone)
Comparator	Methadone
Outcomes	Comparative clinical effectiveness (detoxification, achieving opioid abstinence, relief of withdrawal symptoms), safety and harms, guidelines and recommendations (length of detoxification time)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies, evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications or included in a selected systematic review, or were published prior to 2009.

Critical Appraisal of Individual Studies

The quality of the RCT was evaluated using the Downs and Black instrument.[10] The guideline was assessed for quality using the Appraisal of Guidelines for Research and Evaluation II (AGREE II).[11]

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 234 citations. Upon screening titles and abstracts, 226 citations were excluded and 8 potentially relevant articles were retrieved for full-text review. An additional three potentially relevant reports were identified through grey literature searching. Of the 11 potentially relevant reports, two reports were included in this review. The study selection process is outlined in a PRISMA flowchart (Appendix 1). One RCT and one evidence-based guideline met inclusion criteria.

Summary of Study Characteristics

Details of study characteristics are provided in Appendix 2.

The open-label RCT was conducted in the United States.[12] This study enrolled 54 patients with nonmalignant chronic pain related to the spine or a large joint and an addiction to prescription opioids. The mean age of the patients was 38.3 years and the majority of patients (59.3%) had abused hydrocodone. Patients were randomized to receive a daily dose of Suboxone or methadone for a treatment period of six months. Reported outcomes included treatment retention and opioid use as reported by the patient or analyzed by urine test.

The guideline was published by the US Department of Veterans Affairs with the objective of improving outcomes for adult patients with substance use conditions of any severity. The

guideline did not focus specifically on patients with addiction to prescription opioids, but this patient group was also included in the target population.

Summary of Critical Appraisal

Details of critical appraisal are provided in Appendix 3.

The RCT reported an adequate method of randomization and patients who did not complete the treatment regimen were documented. Drop-out rates were similar between treatment groups. Only participants who completed the treatments were included in the analyses, which may have biased the results. The patient and outcome assessors were not blinded to treatment. In addition, a power calculation to determine an appropriate sample size was not reported.

The guideline was developed by a working group that included individuals from relevant professions (including primary care, internal medicine, psychiatry, psychology, psychotherapy research, social science research, pharmacy, and nursing). The guideline development methodology was reported and had clearly defined objectives and target populations. The literature search methodology was not reported in detail. The recommendations were directly linked to evidence and both recommendations and evidence were graded according to defined criteria. Patient views and preferences were not directly sought and potential barriers and cost implications of applying the recommendations were not considered.

Summary of Findings

Details on study findings are provided in Appendix 4.

<u>What is the comparative clinical effectiveness and safety of Suboxone versus methadone when used as a tool for detoxification in patients addicted to prescription opioids?</u>

In the open-label RCT, 26 patients completed the six month treatment with Suboxone or methadone (48.1%, 13 per group). The mean age of the patients who completed the study was 36 years. The median and range of ages was not reported. This study found that both Suboxone and methadone were able to reduce abuse of other opioids in patients with severe nonmalignant chronic pain.[12] Patients receiving methadone treatment reported less use of illicit opioids than patients receiving Suboxone after six months of treatment ($P = 0.039$). Opioid use as determined by positive urine test, however, was not statistically significantly different between treatment groups (Suboxone 5 patients versus methadone 2 patients; $P > 0.05$). Both Suboxone and methadone had similar safety profiles.

<u>What is the comparative clinical effectiveness of Suboxone versus methadone in achieving complete opioid abstinence in patients addicted to prescription opioids?</u>

No evidence on the comparative clinical effectiveness of Suboxone versus methadone in achieving complete opioid abstinence in patients addicted to prescription opioids was identified. The RCT reported outcomes after six months of continuous treatment at the first follow-up visit, at which point patients were permitted to choose to begin an abstinence-oriented treatment plan, initiate a tapering schedule leading to opioid discontinuation, continue Suboxone or methadone treatment, or return to using their previous opioids.[12] Longer-term results beyond the first follow-up were not reported.

What is the comparative clinical effectiveness of Suboxone versus methadone for the relief of withdrawal symptoms and cravings in patients addicted to prescription opioids for less than 12 months?

No evidence on the comparative clinical effectiveness of Suboxone versus methadone for the relief of withdrawal symptoms and cravings in patients addicted to prescription opioids for less than 12 months was identified.

What is the comparative clinical effectiveness of Suboxone versus methadone for the relief of withdrawal symptoms and cravings in patients addicted to prescription opioids who continue to frequently misuse central nervous system depressants?

No evidence on the comparative clinical effectiveness of Suboxone versus methadone for the relief of withdrawal symptoms and cravings in patients addicted to prescription opioids who continue to frequently misuse central nervous system depressants was identified.

What are the guidelines associated with the length of detoxification time using Suboxone in patients addicted to prescription opioids?

The US Department of Veteran Affairs' clinical practice guideline for management of substance use disorders (2009) recommends that "methadone or sublingual buprenorphine/naloxone maintenance as first line treatments due to their documented efficacy in improving retention and reducing illicit opioid use and craving." This statement was rated as a Strong Recommendation. With regards to the length of detoxification time using Suboxone, the guideline states that "within 1 to 3 days, a daily dose of buprenorphine/naloxone should be achieved that eliminates signs and symptoms of opioid withdrawal, suppresses opioid craving, and eliminates illicit opioid use; this dose could range from 2 mg buprenorphine/0.5 mg naloxone per day to 16 mg buprenorphine/4 mg naloxone per day and would rarely exceed that amount." (No strength for this recommendation was provided).

Limitations

There was one study identified that included patients that were addicted to prescription opioid and not heroin or other illicit drugs. The RCT enrolled a relatively small sample size (N = 54) with no power calculation reported, and a high loss to follow-up resulted in fewer patients included in the analysis (N = 26). This study enrolled patients who were older than 18 years, and not all patients were under 30 years of age, the population of interest in this review. The RCT dosed patients with a range of Suboxone doses, with the average daily dose falling within the higher end of the range, limiting generalizability of the results to patients who take lower Suboxone doses.

No Canadian studies or guidelines were identified, limiting applicability to the Canadian context.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

A CADTH Rapid Response report was published in 2013 that examined the comparative clinical effectiveness of Suboxone and methadone for the treatment of patients with opioid dependence.[13] That report found that Suboxone and methadone had similar clinical effects on retention in treatment and heroin use among adult patients with opioid dependence.

This report focused only on patients who had an addiction to prescription opioids. One randomized controlled trial found that both Suboxone and methadone were similar with regards to treatment retention and decreasing use of other opioids in patients with nonmalignant chronic pain and an addiction to a prescription opioid. The results should be interpreted with caution due to the small sample size, high discontinuation rates, and relative short duration of study. Patients enrolled in this study were not necessarily young adults, as the mean age was over 30 years, limiting the applicability of the results to a younger population.

One guideline suggests that a daily dose of Suboxone for 1 to 3 days should eliminate signs and symptoms of opioid withdrawal, suppress opioid cravings, and eliminate illicit opioid use in adults. This guideline was not specific to patients addicted to prescription opioids, but targeted adult patients with any substance use condition.

No Canadian studies or guidelines were identified.

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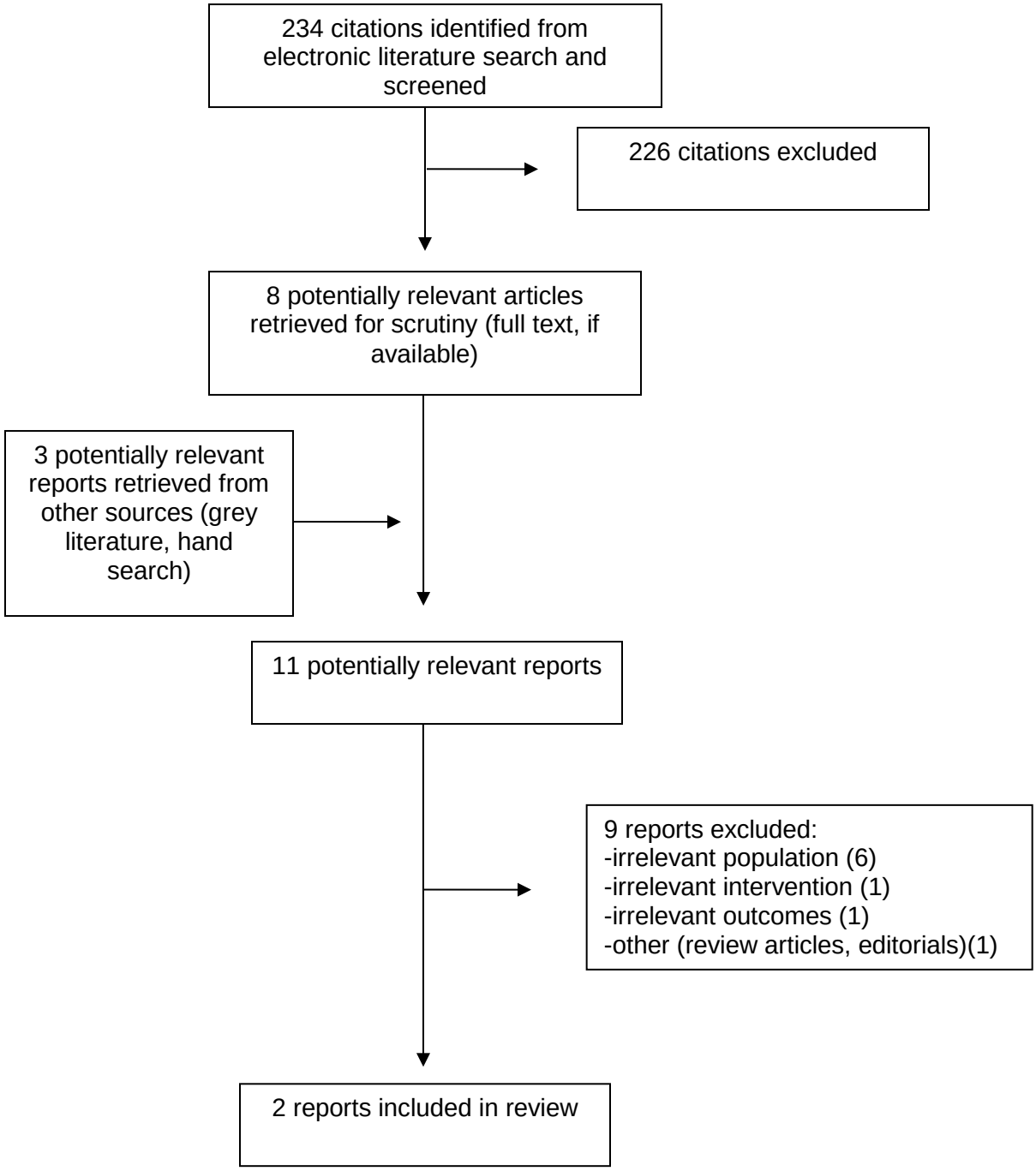
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Study Characteristics

Characteristics of included RCTs

First Author, Publication Year, Country	Study Design and Length	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
Neumann et al (2013)[12] USA	Open-label RCT 6 months	54 patients (mean age 38.3 years, 53.7% male) with nonmalignant chronic pain related to the spine or a large joint (hip, knee, shoulder) and an addiction to prescription opioids (59.3% Hydrocodone, 14.8% Oxycodone, 9.3% Fentanyl, 3.7% Heroin, 1.9% Morphine, 1.9% Codeine)	Suboxone (4-16 mg/day buprenorphine, 1-4 mg/day naloxone), sublingual (n = 26) Average daily dose: 14.93/3.73 mg	Methadone (10-60 mg/day), oral (n = 28) Average daily dose: 29.09 mg	Treatment retention, opioid use (self-report or urine test)

Characteristics of included evidence-based guidelines

First Author, Publication Year, Country	Objective	Target Population	Outcome
Department of Veterans Affairs (2009)[14] USA	To improve outcomes for patients with substance use conditions (cessation or reduction of substance use, reduction in occurrence and severity of relapse, improved psychological and social functioning and quality of life, improved co-occurring medical and health conditions and reduction in mortality).	Adult patients with substance use conditions treated in any Department of Veterans Affairs/Department of Defense clinical setting, including patients who have both substance use and other health conditions; patients with any level of severity.	Quality of life, symptoms, retention, co-occurring conditions, mortality, adverse effects.

APPENDIX 3: Summary of Critical Appraisal

First Author, Publication Year, Study Design	Strengths	Limitations
Neumann et al (2013)[12] RCT	• Method of randomization described. • Description of losses to follow-up.	• Power calculation to determine sample size was not reported. • Patients and outcome assessors were not blinded. • ITT analysis was not performed.
Department of Veteran Affairs (2009)[14] Guideline	• Clearly defined objectives, scope and target populations • Guideline development group included individuals from relevant professional groups. • Guideline development methodology described. • Recommendations are directly linked to evidence.	• Patients' views and preferences were not directly sought. • Potential barriers of applying the recommendations not considered. • Cost implications of applying the recommendations not considered.

APPENDIX 4: Summary of Findings

Summary of RCTs

<table>
<tr><th>First Author, Publication Year</th><th>Main Study Findings</th><th>Authors' Conclusions</th></tr>
<tr><td>Neumann et al (2013)[12]</td><td><u>Comparison of SUB versus MET in patients with chronic pain + opioid addiction at 24 weeks</u>
13 patients in each group completed the study

<table><tr><th>Outcome</th><th>SUB</th><th>MET</th><th>P value</th></tr><tr><td>Positive urine test for opioids, n (%)</td><td>5 (38.5)</td><td>2 (15.4)</td><td>NS</td></tr><tr><td>Self-reported opioid use, n (%)</td><td>5 (38.5)</td><td>0</td><td>0.039</td></tr><tr><td>Treatment retention, n (%)</td><td>13 (50.0)</td><td>13 (46.4)</td><td>NS</td></tr><tr><td>Self-reported side effects, n (%)</td><td>8 (61.5)</td><td>9 (69.2)</td><td>NS</td></tr></table>
After 6 months treatment, no patients in the MET group compared to 5 in the SUB group reported illicit opioid use; other differences between the two groups were not significant.</td><td>"We conclude that both buprenorphine/naloxone and methadone treatment for 6 months reduce nonmalignant chronic pain in participants with coexisting opioid addiction. Patients receiving methadone treatment reported less use of other opioids at 6 months than participants receiving buprenorphine/naloxone treatment, but buprenorphine has a better safety profile." (p. 76-77)</td></tr>
</table>

Summary of guidelines

First Author, Publication Year	Recommendations
Department of Veteran Affairs (2009)[14]	"Strongly recommend methadone or sublingual buprenorphine/naloxone maintenance as first line treatments due to their documented efficacy in improving retention and reducing illicit opioid use and craving." [Good quality evidence, strong recommendation] "Buprenorphine target dose is generally up to 16 mg daily; doses above 32 mg are rarely indicated. In all cases, except pregnancy, the combination product of buprenorphine/naloxone should be used." [Poor quality evidence] "Medically supervised opioid withdrawal is rarely effective as a long-term strategy for treatment of opioid dependence because of high relapse rates. Opioid maintenance with buprenorphine/naloxone or methadone is the definitive treatment of choice in most cases." [Fair quality evidence] Withdrawal using buprenorphine/naloxone: • Only physicians with a waiver from the US Department of Health and Human Services can prescribe buprenorphine/naloxone • Initial stabilization is accomplished via induction with buprenorphine/naloxone just as it would be for maintenance with this agent (See Table S-1 in the original guideline). To reduce the risk of precipitated withdrawal, the patient must be in sufficient opioid withdrawal to be manifesting objective signs of withdrawal prior to starting

First Author, Publication Year	Recommendations
	buprenorphine/naloxone usually at least 8 hours since the patient's last use of heroin or other short-acting opioid or at least 24 and preferably at least 48 hours have elapsed since the last use of methadone or other long-acting opioid • Within 1 to 3 days, a daily dose of buprenorphine/naloxone should be achieved that eliminates signs and symptoms of opioid withdrawal, suppresses opioid craving, and eliminates illicit opioid use. This dose could range from 2/0.5 mg per day to 16/4mg per day and would rarely exceed that amount • Once stabilization has been achieved the dose can be rapidly tapered over 5 to 7 days. There is little evidence that prolonging the taper leads to better results. (If the patient and physician prefer a longer taper, there is also no evidence that a longer taper is harmful).