Primary Care versus Specialty Care Management of Opioid Use Disorder

by

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ABSTRACT

With the rise of opioid use over the past several decades, both medicinal and recreational, the incidence of opioid use disorder has also increased. Opioid use disorder, previously described as "opioid abuse or dependence" in the DSM IV, can lead to loss of family, employment or life. While first-line pharmacotherapy management of opioid use disorder has been well described in guidelines with initiation of long-acting opioid agonists, the optimal setting of treatment has not been well defined. Traditionally, patients living with opioid use disorder have been treated in specialty care centers, settings equipped specifically for those living with opioid or other drug dependence. However, the possibility of treatment in a primary care setting has not been thoroughly explored.

The objective of this research was to identify if treatment of opioid use disorder in primary care was equivalent or superior to treatment in a designated specialty care setting. A systematic review was conducted in order to identify randomized controlled trials that compared these two treatment settings. Seven relevant databases were searched and after dual title/abstract and full-text review, studies were included if they enrolled patients with opioid use disorder and compared opioid agonist therapy in a primary care and specialty care setting. Six trials of 493 patients conducted in two countries met inclusion criteria. Meta-analyses were conducted on our two primary outcomes: opioid abstinence and treatment retention. The proportion of opioid-abstinent patients was significantly higher in primary care (55%) compared to patients in specialty care (34%; p=0.04). Rates of retention were not statistically significant between groups, although trended in favour of primary care (80% versus 63%; p=0.08). Individual studies found higher patient satisfaction more often in primary care (77%) than in specialty care (38%) with

70% of patients reporting preference for treatment in primary care settings (21% specialty care, 9% no preference).

In conclusion, I found a significant improvement in opioid abstinence for patients being treated in primary care with more patients reporting higher satisfaction and preference for primary care settings. Three of the six included trials enrolled patients who were previously stabilized on opioid agonist therapy in specialty care, and therefore compared treatment maintenance in patients with opioid use disorder during the study period. Regardless of this possible bias favouring specialty care, a non-statistical trend towards benefit in treatment retention in primary care was found. These results suggest that with proper training and support, primary care is equipped to manage patients with opioid use disorder. Future research in this area should focus on patients with opioid use disorder who are less stabilized and include primary care settings more similar to those in Canada.

PREFACE

Some of the research conducted for this thesis was funded by the Alberta College of Family Physicians through the Primary Health Care Opioid Response Initiative, an initiative supported by Alberta Health to counter Alberta's opioid crisis with increased supports and treatment in primary care.

The primary products of this funding were 1) a PEER Systematic Review of Systematic Reviews (Korownyk 2019) and 2) an associated primary care guideline (Korownyk 2019). Both documents, mentioned in Chapters 1 and 2, were conducted by the PEER team, a small group of primary-care professionals supported through the Alberta College. As a member of the PEER team, I contributed to the data collection, review, analysis and discussion for all sections. I was also the lead reviewer for the section comparing the effect of primary care versus specialty care setting on patient outcomes, supported by Dr. Garrison. A separate summary of this work, for which I was lead author, was distributed by the Alberta College of Family Physicians to over 34,000 Canadian family physicians as an e-mail "Tools for Practice", and published in Canadian Family Physician – a journal provided to all Canadian Family Physicians by the College of Family Physicians of Canada.

Chapter 1 Publication:

Korownyk C, Perry D, Ton J, Kolber MR, Garrison S, Thomas B, et al. Managing opioid use disorder in primary care. PEER simplified guideline. Can Fam Physician. 2019;65(5):321-30.

Chapter 2 Publications:

Korownyk C, Perry D, Ton J, Kolber MR, Garrison S, Thomas B, et al. Opioid use disorder in primary care. PEER umbrella systematic review of systematic reviews. Can Fam Physician. 2019;65(5):e194-e206.

Perry D, Garrison S. Location, location, location: Treating patients with opioid use disorder in primary care. Tools for Practice. 2018. Available at: https://gomainpro.ca/wp-content/uploads/tools-for-practice/1538762474_tfp221primarycareoudfv.pdf.

After the systematic review of systematic reviews was completed, recognizing there was a clinically impactful finding, I sought and obtained approval to conduct a full Cochrane Systematic Review of individual RCTs on this topic. This Cochrane Systematic Review is described in detail in Chapter 3. The protocol has been published and the full review is under peer review by the Cochrane working group. The archived Tools-for-Practice summary (citation to webpage) has also been updated by me with the more comprehensive information the Cochrane Systematic Review provided. I led and participated in all aspects of the Cochrane review process, and I wrote both the protocol, and the full review, with the editorial feedback of Dr. Garrison, Dr. Kirkwood, Dr. Korownyk and Dr. Ton. The Cochrane managing editor, Zuzana Mitrova, developed the search strategy and provided the titles and abstracts for review based on our developed research question. Dr. Garrison, Dr. Ton and I conducted the dual title/abstract review, dual full-text review and dual data extraction. I performed all analyses.

Chapter 3 Publication:

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1 CHAPTER 1: INTRODUCTION

1.1 STATEMENT OF THE PROBLEM

Pain is a common presenting concern in healthcare. In Canada, approximately 1 in 5 adults live with chronic pain.[1] Both acute and chronic pain can be challenging to manage, and for over 30 years, opioids were marketed as the cure for pain. While there is some evidence to support the short-term use of opioids in the treatment of acute pain,[2-4] an increasing body of evidence in chronic pain suggests no substantial benefit[5-6] and a myriad of harms, including hyperalgesia, nausea, vomiting, constipation, sedation, dependence, overdose and death.[7]

North America is facing an opioid crisis, with over 9,000 Canadians having lost their lives to opioid-related harms between 2016 and 2018.[8] In Canada during the first two months of 2020, over 4500 opioid-related overdoses were reported over nine provinces.[9] Alberta, British Columbia and Ontario comprised 86% of all opioid-related deaths in the country during the first half of 2020.[9] While illicit street opioids are still responsible for approximately 75% of overdose-related deaths[9], prescription opioids continue to play a role. From 2013 to 2018, we have seen a 2% absolute decrease in the proportion of Canadians prescribed opioids (14.3% to 12.3%). This may be due, in part, to updated guidelines and specific recommendations, increased education and awareness, provincial prescription monitoring programs and the release of tamper-deterrent oxycodone.[10] Some providers, however, continue to prescribe opioids in large quantities and for long durations, potentially leading to dependence in the patient or dependence in others, through diversion.[11] A US case-control study found an association between opioid prescriptions in family members and overdose in family members who were not prescribed opioids.[12]

Providing comprehensive and appropriate care to patients living with opioid use disorder is crucial in preventing opioid-related harms and mortality and to support recovery. Care for patients with opioid use disorder is complex. It requires management of pharmaceutical interventions (i.e., opioid agonist therapy) but can also include treatment of other comorbid conditions and referrals to counseling, physiotherapy, complementary services to manage chronic pain, and social work for employment or family needs. While patients have access to free specialty services in Canada, admittance often comes after substantial wait-times. Further, if paid programs are a second option, cost is often a barrier. The Canadian Centre for Addictions estimates the cost for private therapy in a Canadian residential treatment program to be anywhere from $300 to $700 per day.[13] There is a need for more sustainable care for patients with opioid use disorder, which prompts the question of whether primary care is equipped to provide similar services and support for this patient population.

1.2 OPIOID USE DISORDER

1.2.1 Opioids in the management of pain

Opioids are natural or synthetically-derived chemicals that are often used in the management of pain.[14] Opioids work by creating connections with opioid receptors and when used properly, they have value in treatment of cancer-related and some acute pain conditions.[2,3,15] High-quality evidence, however, is limited to support their long-term use in most chronic pain conditions.[16-17] Adverse effects of opioids include sedation, dizziness, constipation, nausea and vomiting, and increased sweating.[18] Further, opioids can lead to feelings of euphoria or “feeling high”, which can trigger individuals to continue their use, despite the negative consequences.[19]

Opioid prescribing for pain management was not always common practice. A number of important publications led to the resurgence in opioid prescribing for the treatment of pain in the late 1900s. A 1986 publication by the World Health Organization addressed the need for increased pain management strategies for patients with end-stage cancer.[20] While pain management in palliative patients improved, other questions emerged related to management of additional pain conditions. A Canadian psychology professor published an article questioning why opioids were not being considered in chronic pain management.[21] In 1996, important events occurred that have been cited as two of the biggest contributors to our current opioid crisis. First, the American Pain Society released their well-known "Pain as the 5th vital sign" campaign, supported by regulatory bodies and pharmaceutical companies, which encouraged subjectively-reported high levels of pain to be immediately and intensely acted upon.[22] Inadvertently, patients reporting high levels of pain were often treated with opioids in a way to meet the new standards set out by regulatory bodies. Secondly, in 1996, Purdue Pharma introduced Oxycontin, a long-acting opioid that was aggressively marketed and promoted as a safer alternative to short-acting opioids, with less abuse potential.[23] Beyond an extensive multinational marketing strategy, Purdue Pharma also concentrated its marketing, targeting the highest prescribers of opioids in the U.S.A, a subgroup of physicians that could have been less stringent in their opioid prescribing.[23] Purdue also made an unprecedented move when they mass distributed promotional materials related to Oxycontin, including a stuffed Oxycontin pill.[23]

As a result, opioid prescribing continued to rise in the first part of the 1990s, leading to increases in inappropriate use, overdoses and mortality. In the U.S., approximately 450,000 adults died from an opioid overdose between 1999 and 2018.[24] Similarly, in Canada, 16,364 individuals died

from an opioid-related overdose from 2016 to 2020.[9] In 2007, Purdue Pharmaceuticals pled guilty and paid $634 million for misrepresentation of Oxycontin, long-acting oxycodone, which they claimed was less addictive than other opioids.[25] Similarly in 2020, Purdue pled guilty to criminal charges and may pay up to $8 billion, related to their marketing of Oxycontin.[26]

In the midst of an opioid crisis, it is now essential to treat patients living with an opioid use disorder, however diagnosis can be challenging.

1.2.2 Opioid Use Disorder

The Diagnostic and Statistical Manual of Mental Disorders (DSM), 5th edition defines opioid use disorder as: "a problematic pattern of opioid use leading to clinically significant impairment or distress".[27] The term "opioid use disorder" replaced "opioid abuse" and "opioid dependence" in the fifth edition of the DSM , however these terms continue to be used both by healthcare providers and in the literature.

In order to meet diagnostic criteria for opioid use disorder set forth in the DSM, patients must meet at least two of eleven criteria in the past 12 months, including, for example: using increasing doses of opioids over longer timeframes than intended, having failed attempts at controlling opioid use, and having cravings to use opioids.[27] A full list of diagnostic criteria is included in Supplement 1-1.

The severity of opioid use disorder is also scored as mild (2-3 symptoms), moderate (4-5 symptoms) or severe (6 or more symptoms) based on the total number of criteria met.[27]

In patients receiving prescribed opioids, the incidence of opioid use disorder is estimated at approximately 3%,[28] however the incidence varies depending on individual risk factors. Receiving opioids for extended periods (>90 days) or in excessive doses (>120 mg/day morphine equivalents) and a history of opioid or other drug dependence puts individuals at higher risk of developing opioid use disorder.[28] Diagnosis of opioid use disorder in patients with chronic pain is challenging. Tolerance to opioids and presence of withdrawal symptoms, two of the criteria outlined by the DSM, do not apply in the diagnosis of opioid use disorder in patients prescribed opioids for pain management.[27] Although tolerance and withdrawal may be seen in patients using opioids appropriately for chronic pain, or with poor pain management, it is also present in OUD, and determining where the patient falls on the spectrum can at times be difficult to determine. The Prescription Opioid Misuse Index (POMI) is a shorter, six-point screening tool that can be utilized in patients receiving prescription opioids.[29] It has been compared to the DSM and has a strong predictive ability to detect opioid use disorder[30] and provides healthcare providers with a shortened, pain-specific measure to use in their practice. The screening tool is included in Supplement 1-2.

1.2.3 Treatment of Opioid Use Disorder

Following diagnosis, guidelines recommend pharmaceutical management, specifically opioid agonist therapy, for treatment of patients with opioid use disorder.[31-33]

Opioid agonist therapy involves the prescribing of long-acting opioid agonist medications that decrease cravings and help minimize or prevent withdrawal symptoms. Two of the most commonly used medications in Canada include buprenorphine-naloxone and methadone.

Buprenorphine-naloxone, sold under the Trade name Suboxone, is a combination sublingual medication used in the management of opioid use disorder. Buprenorphine is a long-acting partial agonist that attaches to the opioid receptor to control symptoms of withdrawal while also preventing other opioids from attaching to the receptors. Naloxone, an opioid antagonist, prevents overdose if the medication is crushed and injected.[34] The data examining the effect of buprenorphine-naloxone on patient-important outcomes, such as mortality and morbidity is sparse. More common is data on surrogate outcomes in the management of opioid agonist therapy, retention in treatment programs and opioid abstinence. Data from ten randomized controlled trials (2664 patients) found 64% of patients treated with buprenorphine were retained in treatment compared to 39% of patients treated with placebo at 4 to 52 weeks (Risk Ratio 1.66 95% Cl 1.52, 1.82).[35] A 2016 systematic review found self-reported opioid use to be significantly lower in patients randomized to buprenorphine compared to placebo, detoxification or psychotherapy (3 RCTs, 204 patients; 37% versus 60%; Risk Ratio 0.54 95% Cl 0.31, 0.93).[36] Opioid-positive urine samples, a more objective measure of abstinence, were also lower in buprenorphine treated patients compared to placebo, detoxification or psychotherapy, however the difference was not as pronounced (3 RCTs, 206 patients; 40% versus 61%; Risk Ratio 0.63 95% Cl 0.43, 0.91).[36]

Methadone is a full opioid agonist that is also used to minimize and prevent withdrawal symptoms.[37] Methadone has been available in Canada since the 1960s and has traditionally been the mainstay treatment for opioid use disorder. Because it has been available longer, a small body of evidence examining patient-important outcomes is available. Four randomized controlled trials in 576 patients, found a non-significant trend in favour of methadone, compared

to no methadone for reduction in mortality (1% versus 2.8%; RR 0.48 95% Cl 0.10, 2.39).[38] Patients treated with methadone are also more likely to be retained in treatment, compared to those not receiving methadone (73% versus 22%; 6 RCTs, 1,114 patients).[35] Finally, patients treated with methadone are also less likely to test positive for opioids with hair or urine samples than those not treated with methadone (53% versus 78%; 4 RCTs, 793 patients).[35]

Comparatively, both methadone and buprenorphine lead to improvements in treatment retention and opioid abstinence among patients with opioid use disorder. The majority of randomized controlled trials for both methadone and buprenorphine have not examined clinically meaningful outcomes, including non-fatal overdoses, hospitalizations, emergency department visits and disease transmission. Additionally, the methadone literature is not current, with many studies being conducted 20-30 years ago. This adds to the uncertainty of the presented evidence as many of the trials are at risk of bias and employ fixed doses of methadone, a practice not commonly used.[35]

Beyond patient preference, additional limitations exist that may influence healthcare providers to prescribe one opioid agonist over the other. For example, according to the Canadian Narcotic Control Regulations, methadone can only prescribed or administered by a healthcare provider (i.e., physician or nurse practitioner) who has obtained an exemption under section 56 of the Controlled Drugs and Substances Act.[39] Buprenorphine-naloxone does not fall under this restriction and can be prescribed and administered by any licensed physician or nurse practitioner.

Provincially, additional training or resource requirements vary for prescribing methadone. In Alberta, methadone prescribers are required to complete a methadone maintenance treatment workshop, recognized by the College of Physicians and Surgeons of Alberta, and have experience with or training in treatment of patients with opioid use disorder.[39] Alternatively, the province sets out recommendations for providers wishing to prescribe buprenorphine, including the completion of an accredited course.[39] For physicians, these recommendations are not mandatory to prescribe buprenorphine.

Finally, induction and maintenance of methadone and buprenorphine-naloxone differ significantly. While buprenorphine-naloxone induction requires patients to be in active withdrawal, methadone allows patients to be immediately inducted, potentially influencing some patients to choose the latter. Particularly, in patients who are pregnant, the absence of a withdrawal period is preferred to avoid withdrawal symptoms from negatively affecting the fetus.[31] In a more generalized population, buprenorphine induction is considerably faster (1-4 days) and easier to maintain, with more opportunity for take-home dosing.[33] Finally, buprenorphine-naloxone is associated with potentially less side effects, lower risk of overdose and diversion due to its chemical profile (i.e., partial agonist) and the addition of naloxone.[33] An example buprenorphine induction protocol is included in Supplement 1-3.

It should be noted that initiation and maintenance of opioid agonist therapy can be accomplished in different treatment settings. Maintenance of pharmaceutical therapy, without initiation is still defined as treatment of opioid use disorder.

Pharmaceutical intervention with opioid agonist therapy is necessary for patients with opioid use disorder in order to reverse negative consequences of the disorder, including stabilization of a

patient's personal and professional life, reduction in withdrawal symptoms and prevention of severe outcomes, including unintentional overdose and death.

1.3 TREATMENT SETTINGS

1.3.1 What constitutes primary care?

According to the World Health Organization, primary health care is a "whole-of-society approach to health and well-being centered on the needs and preferences of individuals, families and communities".[40] In 1978, the celebrated Declaration of Alma-Ata was adopted at the International Conference on Primary Care, which acknowledged the significance of primary care and called governments to action to introduce primary care globally.[41] Today, primary care is recognized as the center of care for all individuals. Providers care for patients across the lifespan, addressing promotive, preventive, curative, rehabilitative and palliative needs as they develop.[40]

In Canada, primary care is recognized as the first point of access for patients within the healthcare system. It is also recognized as promoting continuity and centrality, ensuring that regardless of where and how patients move through the healthcare system, the central connecting point remains with their primary care provider.[42] In Alberta, contacts with family physicians every month are approximately 234 per 1000 people compared to only 63 per 1000 for specialist physicians, highlighting the large scope of care provided by primary health care.[43] In addition to managing a larger patient volume than their specialist colleagues, primary care's responsibility to individuals across the lifespan strengthens their ability to treat patients with complex healthcare needs, including comorbid or mental health conditions.[44]

Who provides primary care services can differ depending on country, patient population and community resources. Family physicians, nurse practitioners and other allied health professionals

often provide team-based care in Canadian primary care settings. Unsurprisingly, countries with the lowest burden of health care needs are represented by the largest number of healthcare providers while developing countries where health care burden is immense have fewer healthcare providers.[45] When considering the importance of primary health care in the promotion of health and prevention of disease, it stresses the need for more primary health care providers in countries still struggling with the consequences from vaccine-preventable illnesses.

While the challenges faced by developing countries should not be overlooked, primary care models in developed countries have been linked to overall improved health,[46] decreased mortality[47-48] and increased healthcare savings.[40]

1.3.2 What constitutes specialized care?

Specialized care of opioid use disorder can differ substantially based on type of program, geographic region, and funding model.

Types of specialized care programs for patients with opioid use disorder are dependent on the individual's goals for treatment. Harm reduction strategies, including access to clean needles, naloxone kits or supervised consumption sites are tailored for individuals who intend to continue using illicit opioids, however would like to reduce their risk of overdose or transmission of disease.[33,49] More relevant to this dissertation, is the provision of opioid agonist therapy (both initiation and maintenance of treatment) to patients seeking management of their opioid use disorder.

Specialized opioid use disorder programs often employ a comprehensive variety of healthcare professionals with experience and training in the care of patients with substance use disorders.

This can include psychiatrists, addictions-trained physicians and allied health professionals, psychologists, and social workers. Healthcare professionals work together to support a patient's health needs, including induction and maintenance on opioid agonist therapy, counseling and resources to support education or employment needs.

Admittance to timely opioid agonist therapy in specialized programs remains a challenge. The Canadian Mental Health Association approximates wait-times for specialized treatment to be 2 to 52 weeks, depending on location and type of program. Furthermore, publicly funded programs had longer wait times than privately funded programs.[50] In Alberta, privately funded programs are associated with an out of pocket expense for patients, ranging from $20 to $200 per day.[51] A recent Canadian survey of stakeholders involved in the care of patients with opioid use disorder highlighted associated stigma with specialized care, inadequate transportation, geographic location of specialized facilities, difficulties in scheduling and office hours, insufficient staffing, and restrictions in funding and training as continuing challenges in specialized treatment settings.[52]

1.4 SUMMARY

Increases in opioid prescriptions over longer durations combined with the addictive properties of the drug have contributed to our current opioid crisis. Every year, thousands of individuals suffer personal and professional ramifications, including accidental overdose or death, due to opioid use disorder. Our present climate emphasizes the need for more comprehensive, accessible treatment for patients with opioid use disorder.

Specialty care services offer ample support to patients seeking treatment, including first line pharmaceutical management with buprenorphine or methadone, however immediate accessibility

for an increasing number of patients with opioid use disorder is becoming a challenge. Accessibility is limited by wait-times in publicly funded settings and cost in privately funded programs.

Primary health care has demonstrated competence in management of all individuals across the lifespan, including those living with complex health needs and comorbidities. The increasing need for services in opioid use disorder management and the validated success of primary care raises the question of what role can primary care play in the management of these complex patients.

1.5 OBJECTIVES

The proposed research aimed to determine:

1. Whether treatment of opioid use disorder, through maintenance of opioid agonist therapy (with or without initation of medication), in primary care as compared to the traditional specialty care setting results in equivalent or improved outcomes for retention in treatment, reduction in opioid use, and other patient-oriented outcomes.

From this review, findings were and will be disseminated in two formats:

1. To primary care health professionals through an online summary tool, Tools for Practice (Chapter 2).
2. In a more traditional format, as a published systematic review, through the Cochrane Collaboration of Systematic Reviews (Chapter 3).

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Supplement 1-1: DSM Opioid Use Disorder Criteria

DSM-5 Criteria for Diagnosis of Opioid Use Disorder

Diagnostic Criteria*
These criteria not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

Check all that apply

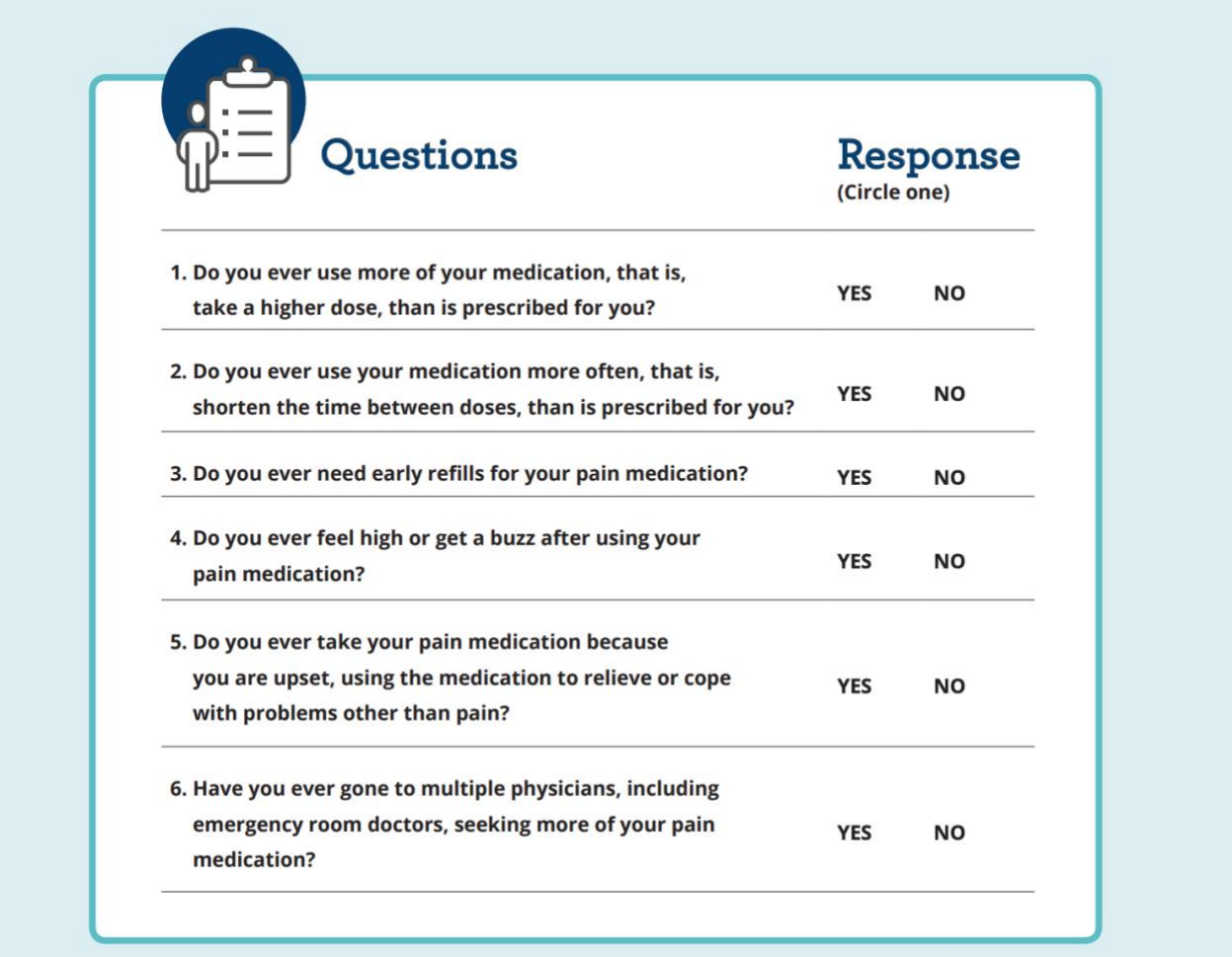
	Opioids are often taken in larger amounts or over a longer period of time than intended.
	There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
	A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
	Craving, or a strong desire to use opioids.
	Recurrent opioid use resulting in failure to fulfill major role obligations at work, school or home.
	Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
	Important social, occupational or recreational activities are given up or reduced because of opioid use.
	Recurrent opioid use in situations in which it is physically hazardous
	Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.
	*Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of opioids to achieve intoxication or desired effect (b) markedly diminished effect with continued use of the same amount of an opioid
	*Withdrawal, as manifested by either of the following: (a) the characteristic opioid withdrawal syndrome (b) the same (or a closely related) substance are taken to relieve or avoid withdrawal symptoms

Total Number Boxes Checked: _____

Severity: **Mild**: 2-3 symptoms. **Moderate**: 4-5 symptoms. **Severe**: 6 or more symptoms

*Criteria from American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,. Washington, DC, American Psychiatric Association page 541. For use outside of IT MATTTRs Colorado, please contact ITMATTTRsColorado@ucdenver.edu

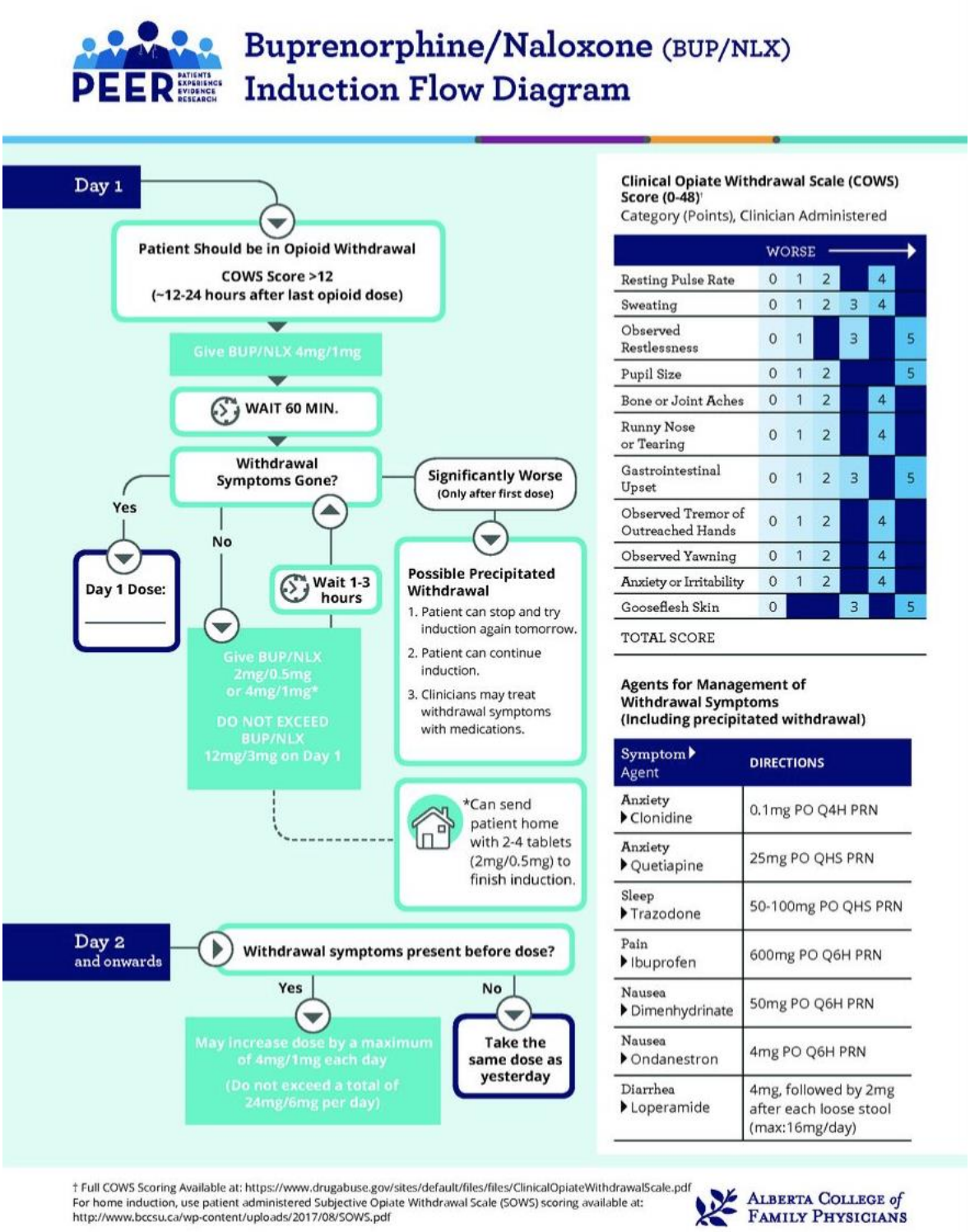
Supplement 1-2: Prescription Opioid Misuse Index (POMI)



Questions	Response (Circle one)	
1. Do you ever use more of your medication, that is, take a higher dose, than is prescribed for you?	YES	NO
2. Do you ever use your medication more often, that is, shorten the time between doses, than is prescribed for you?	YES	NO
3. Do you ever need early refills for your pain medication?	YES	NO
4. Do you ever feel high or get a buzz after using your pain medication?	YES	NO
5. Do you ever take your pain medication because you are upset, using the medication to relieve or cope with problems other than pain?	YES	NO
6. Have you ever gone to multiple physicians, including emergency room doctors, seeking more of your pain medication?	YES	NO

Reference: Korowynk C, Perry D, Ton J, Kolber MR, Garrison S, Thomas B, et al. Managing opioid use disorder in primary care. PEER simplified guideline. Can Fam Physician. 2019;65(5):321-30.

Supplement 1-3: Buprenorphine Induction Recommendations



Reference: Korowynk C, Perry D, Ton J, Kolber MR, Garrison S, Thomas B, et al. Managing opioid use disorder in primary care. PEER simplified guideline. Can Fam Physician. 2019;65(5):321-30.

2 CHAPTER 2: MANAGEMENT OF OPIOID USE DISORDER: TOOLS FOR PRACTICE

2.1 INTRODUCTION

Continued professional development is defined as the process of professionals maintaining and improving their knowledge and skills on a continual basis, often throughout their career.[1] Continued professional development (CPD) plays an important role in healthcare, a continuously evolving profession. The College of Family Physicians of Canada house MainPro+, an accreditation program that tracks family physicians required CPD credits and reviews all new CPD programs to determine if they meet eligibility criteria to be considered "certified" (e.g., free from pharmaceutical support, ethically sound, relevant content with opportunities for interactivity).[2] In Canada, family physicians are required to report 25 credits annually and 250 credits (125 certified) over a five year cycle.[3] CPD in healthcare can directly impact patient care. A 2013 retrospective data analysis found family physicians who participated in more hours of CPD scored better in all "high-quality" care categories (i.e., record keeping, investigation, diagnosis and treatment) during inspection visits.[4] Similarly, an analysis of 617 Canadian primary care physicians found an association between participation in CPD with improved performance on practice assessments.[5]

One method of providing CPD to improve physician practice and patient care is the creation and dissemination of clinical summaries and decision aids. A recent Cochrane review found that printed and published education materials improved the quality of healthcare professionals' practice and the quality of patient care.[6] Didactic education continues to be the most widely utilized format for CPD[7-8] and clinical summaries and decision aids represent two didactic

models that support healthcare professionals' learning styles[9] and provide physicians with a digestible quantity of information that they can apply in their practice.

In 2019, family physicians represented 50-53% of the 91,000 practicing physicians in Canada.[10] In addition to providing the majority of healthcare in Canada, individual family physicians manage high caseloads and provide holistic, comprehensive care to a patient population that spans the entire lifespan. It is important to develop clinical summaries and decision aids for family physicians that are concise, relevant to primary care, provide evidence-based updates and that can be easily implemented into practice.

Tools for Practice (TFP) is an Alberta-led initiative that strives to provide brief evidence-based summaries of topics relevant to primary care in Canada.[11] Tools are released on a biweekly basis and emailed to approximately 39,000 family physicians and allied healthcare professionals nationally. Tools for Practice are also a MainPro+ activity, where physicians can earn certified CPD. To earn credits, physicians read the tool and answer a number of reflective questions to test their understanding of the content. Tools for Practice is a reliable resource that improves access to evidence updates for family physicians. In a recent review of published TFPs, 95% of 143 contributing authors worked in primary care and over 99% were conflict of interest free, receiving no monetary support from industry or organizations that could lead to potential biases.[12]

The objective of this dissemination was to utilize a trusted, conflict-free resource to deliver physicians with pertinent, evidence-based information related to treatment settings for patients with opioid use disorder while providing access to certified CPD to further improve their practice and patient care.

2.2 METHODS

This clinical summary was developed from randomized controlled trial evidence comparing the treatment of patients with opioid use disorder in primary versus specialty care settings. This evidence was also published by the Canadian Family Physician in the PEER Systematic review of systematic reviews, a comprehensive umbrella review that examined multiple aspects of treatment of opioid use disorder in a primary care setting.[13] Development of the tool followed a standardized set of guidelines, delineated by PEER, the creators of Tools for Practice.[14]

After the initial version was drafted, the tool was peer reviewed by several primary care healthcare providers in the community. Any recommendations and questions were addressed in the final editing stage.

The original tool was published in October 2018 and emailed to family physicians and allied healthcare professionals nationally.[15] The original email list has been compiled over the previous ten years and consists of family physicians affiliated with the various provincial chapters as well as any subscribers to Tools for Practice.

The updated tool was developed as a result of the updated findings in the Cochrane Systematic Review, described in Chapter 3 of this dissertation, and replaced the original tool online.

2.3 RESULTS

In Alberta, the Tools for Practice, entitled “Location, Location, Location: Treating patients with opioid use disorder in primary care” was disseminated by email to 5507 family physicians. Of those receiving the summary, 2774 (51.7%) of physicians accessed the tool on the Tools for

Practice website. The original and updated online tool are available in Figure 2-1 and Figure 2-2, respectively.

Nationally, the tool was disseminated to 34,802 physicians with 16,588 further accessing the tool, a 49.26% open rate. 159 physicians also completed the reflective exercise for 0.25 certified credits.

While we considered submitting the updated tool for republication, we chose to issue it as an online replacement only, as the results did not differ significantly from the original publication and to allow for more novel topics to be released.

2.4 DISCUSSION

Clinical summaries such as Tools for Practice provide physicians with pertinent, evidence-based clinical content to inform practice while providing information to encourage shared informed decision making with their patients.

A substantial number of physicians accessed this clinical summary; however, we are unsure in what capacity they are implementing care for patients with opioid use disorder in their practice. Regardless of implementation, this Tools for Practice provided a brief educational opportunity to a large proportion of physicians with a small proportion taking advantage of the certified learning options.

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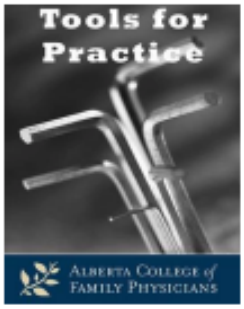
Figure 2-1: Tools for Practice (Original)

Tools for Practice is proudly sponsored by the Alberta College of Family Physicians (ACFP). ACFP is a provincial, professional voluntary organization, representing more than 4,800 family physicians, family medicine residents, and medical students in Alberta. Established over sixty years ago, the ACFP strives for excellence in family practice through advocacy, continuing medical education and primary care research. www.acfp.ca

October 9, 2018



Location, Location, Location: Treating patients with opioid use disorder in primary care

Clinical Question: How well is opioid agonist therapy managed in primary care?

Bottom Line: For opioid-dependent patients, receiving opioid agonist therapy (OAT) in a primary care setting versus a specialized opioid treatment program results in an additional 1 in 6 patients retained in treatment and abstinent from street opioids at 42 weeks. Additionally, twice as many patients (77% versus 38%) report being very satisfied with their care. All studies had supports and training available to their primary care teams.

Evidence:

- Three randomized controlled trials (RCTs, 46-221 patients)[1-3] compared OAT (methadone or buprenorphine) in primary care versus a specialized opioid treatment program; mean follow-up 42 weeks.
  - Retention in treatment (three RCTs; 287 patients; meta-analyzed by TFP authors):
    - 86% versus 67% specialty care; Number Needed to Treat (NNT)=6.
  - Street opioid abstinence (three RCTs; 313 patients; measured by urine toxicology and/or self-report; meta-analyzed by TFP authors):
    - 53% versus 35% specialty care; NNT=6.
  - Patient satisfaction:
    - Patients "very satisfied" more often in primary care (77% versus 38%; one RCT, 46 patients).[1]
    - Patients report higher satisfaction with information provided in primary care (one RCT; percentages not reported).[2]
  - Withdrawal symptoms:
    - Statistically reduced from baseline, but no difference between groups (one RCT, 46 patients).[3]
  - Adverse events:
    - Not reported.

Context:

- Included populations varied:
  - Patients receiving methadone for at least one year and abstinent from street drugs.[1]
  - Patients not on methadone or switching from buprenorphine.[2]
  - Patients on a methadone waitlist with an opioid-positive urine screen.[3]
  - In two studies, primary care providers were general internists.[1,3]
- Supportive teams and training were used in the above RCTs:
  - Primary care settings were largely team-based.[1,3]
  - Support/training was available.[1,2]
  - One primary care clinic was affiliated with a substance misuse clinic.[3]
  - One study enrolled only physicians with experience in treating opioid/other drug dependence.[2]
  - One study provided physicians with training and 24-hour pager support.[1]
- Over 50% of surveyed physicians report inadequate staff support and training, time and office space as barriers to prescribing OAT in their practices.[4,5]

Authors:
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Disclosure:
Authors do not have any conflicts of interest to declare.

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Figure 2-2: Tools for Practice (Updated)

Revision: November 27, 2020
Written: October 9, 2018

ALBERTA COLLEGE of FAMILY PHYSICIANS

THE COLLEGE OF FAMILY PHYSICIANS OF CANADA | LE COLLÈGE DES MÉDECINS DE FAMILLE DU CANADA

PEER

Location, Location, Location: Treating patients with opioid use disorder in primary care

Clinical Question: How well is opioid use disorder (OUD) managed in primary care?

Bottom Line: For patients with OUD, receiving opioid agonist therapy (OAT) in a primary care setting, an additional 1 in 5 patients were opioid abstinent at 46 weeks, compared to patients receiving care in a specialty care setting. Patients were also more satisfied with their treatment and physician explanations in primary care. Rates of retention were similar between groups. Provision of support and/or training was reported consistently throughout the literature

Evidence:

- Six randomized controlled trials (RCTs, 22-221 patients)[1-6] compared OAT (methadone or buprenorphine) in primary care versus specialized opioid treatment; mean follow-up 46 weeks
  - Opioid abstinence (five RCTs; 428 patients; measured by urine toxicology and/or self-report; meta-analyzed by TFP authors):
    - 55% versus 34%; Number Needed to Treat (NNT)=5
  - Retention in treatment (six RCTs; 493 patients; meta-analyzed by TFP authors):
    - 80% versus 63% specialty care; not statistically different
  - Patient satisfaction:
    - Patients were "very satisfied" more often in primary care (77% versus 38%; one RCT, 46 patients)[2], more satisfied with explanations provided by their physicians (numbers not reported; one RCT, 221 patients)[1] and reported higher preference for primary care (70% versus 21% specialty care, 9% no preference)
    - One RCT found similar patient satisfaction between groups[3]
  - Withdrawal symptoms:
    - Statistically reduced from baseline, but no difference between groups[3]
  - Adverse events:
    - One RCT (93 patients) found no difference in emergency department visits or hospitalizations (35% versus 36% specialty care)[4]
    - No other adverse events reported

Context:

- Included populations varied:
  - Patients stabilized for 6-12 months in methadone maintenance programs[2,3,6]

    - Patients not on methadone or switching from buprenorphine[1]
    - Patients recruited from a methadone wait-list or referred[5]
    - Primary care providers varied, including general internists[2,4,5], infectious disease-trained physicians[4], and an addictions-trained physician[3]
- Additional supports were used:
    - Primary care settings were team-based[2-6]
    - Primary care providers had prior training and/or experience[1,4]
    - Support/training was provided[1,2,4,6] and 24-hour pager support[2]
    - Primary care settings were affiliated with or located near a specialty program[1,3,5]
- Over 50% of surveyed physicians reported inadequate staff, training, time and space as barriers to initiating OAT in their practice[7,8]

Authors:

Danielle Perry BScN RN, Scott Garrison MD PhD CCFP

Disclosures:

Authors do not have any conflicts of interest to declare.

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3 CHAPTER 3: PRIMARY CARE VERSUS SPECIALTY CARE MANAGEMENT OF OPIOID USE DISORDER: A SYSTEMATIC REVIEW

3.1 INTRODUCTION

3.1.1 Description of the Condition

The term 'opioids' describes a drug class that activates opioid receptors within the central nervous system. Activating these receptors produces analgesia, with potential side effects including drowsiness and a sense of well-being.[1] While these properties make opioids potentially useful in the treatment of pain, they can also be highly addictive, resulting in their becoming a common drug of misuse. Many people, whether seeking opioids for their potential side effects (i.e. sense of euphoria) or having been prescribed them for pain, now find themselves with an addiction or dependence on opioids (referred to as opioid use disorder, or OUD). A systematic review of over 300,000 participants with pain being treated with opioids for at least seven days (97% for at least three months) found incidence of opioid dependence in highest-quality trials to be approximately 3.1% over two years.[2] Opioid use disorder can lead to disruption in social networks, loss of employment, and adverse health consequences, which include a lethal overdose.[1,3-4] Every day on average, 17 Canadians are hospitalized due to opioid poisoning.[3] Furthermore, the Public Health Agency of Canada reported over 8000 deaths related to opioids between 2016 and 2018.[4]

Recognizing that opioid use disorder is very hard to overcome, the first line of treatment is the initiation of long-acting opioid agonists, a treatment commonly known as OAT (opioid agonist therapy). Using a long-acting opioid decreases the likelihood of entering into opioid withdrawal, which can trigger cravings and opioid use. By decreasing cravings, one's need to obtain opioids is subsequently decreased, and patients stabilize. Evidence suggests that treatment with agonist

therapy may lower morbidity and mortality in people diagnosed with OUD.[5-6] Additionally, the evidence supports an increase in treatment retention, decrease in opioid use in people with OUD, decrease in withdrawal symptoms, and potential reductions in viral infections through the decrease in needle and injection equipment sharing and number of sexual partners.[5-11] Clinics and providers specializing in the treatment of OUD have risen to meet the needs of this population, however medications for OUD remain underused. This may be due in part to limited identification of patients with OUD, or difficulties in accessing specialized clinics. Given that OAT is the mainstay of treatment for this condition, improved access to diagnosis and medical treatment is needed.

3.1.2 Description of the Intervention

According to the World Health Organization (WHO), primary care is a "whole-of-society" approach to health care, ensuring that all individuals, families, and communities receive quality and continuous care across the lifespan.[12] WHO has developed a comprehensive definition of the services primary care should provide. These include: 1) addressing patients' needs through preventive, promotive, curative, rehabilitative, and palliative care, either delivered in primary care or beginning in primary care, with referral to tertiary care services when necessary; 2) addressing all social determinants of health, both within primary care and through development of policy; and 3) encouraging patients to play a role in their own health, which includes promotion of shared, informed decision making.[13] Although the stated goal, not all countries attempt to provide primary care services, and even when primary care is available, the breadth of services vary.

Management of opioid use disorder in primary care would include maintenance of medication, such as opioid agonist therapy, and in some cases, initiation of opioid agonist therapy or access to further psychosocial support. This would also involve providing preventive health services and managing co-morbid health issues that may be unrelated to opioid use disorder. Ideally, a primary care relationship exists prior to the development of opioid use disorder and is enduring despite the development of this condition. In contrast, specialty care management is likely to focus on providing services specific to opioid use disorder, including initiation and maintenance of opioid agonist therapy, counseling and social services, with less or no emphasis on dealing with other health concerns and begins only after opioid use disorder is already established. In settings where care is more integrated and shared between both specialty and primary care providers, we would classify primary and specialty care based on where the majority of care for the patient is provided. For example, in settings where initiation of opioid agonist therapy is provided in specialty care and patients then move into primary care for ongoing maintenance and follow-up, this environment would be classified as primary care.

3.1.3 How the intervention might work

Opioid agonist therapy has been delivered in a wide variety of treatment settings; however, the proportion of patients with OUD who access treatment is small. Data from the United States National Surveys on Drug Use from 2005 to 2013 identified approximately 19% of patients with OUD as having accessed opioid-specific treatment.[14]

The provision of OAT in primary care would allow greater health system capacity for the treatment of opioid use disorder, by providing additional providers and clinics for maintenance and/or initiation of treatment. Offering OAT in primary care may convey additional benefits.

This may be due to 1) potentially less social stigma associated with attending a primary care provider's office; 2) the potential to create a relationship with a primary care provider which the patient may not yet have; and 3) there may be a greater willingness or opportunity on the part of the patient and provider to address co-morbid health concerns.

3.1.4 Why it is important to do this review

If primary care is a viable location to maintain and/or initiate opioid agonist therapy in people with opioid use disorder, there would be greater capacity and resources to manage patients with this condition. To our knowledge, the question of comparing delivery of OAT in primary care versus specialty care has never before been addressed in a systematic review.

3.1.5 Objectives

To determine whether treatment of OUD in primary care as compared to the traditional specialty care setting results in equivalent or improved outcomes for retention in treatment, reduction in opioid use, and other patient-oriented outcomes.

3.2 METHODS

3.2.1 Types of Studies

Randomized controlled trials, including cluster-randomized designs, comparing the treatment of opioid use disorder in primary care and specialty care settings.

3.2.2 Types of Participants

Participants included any community-dwelling adult dependent on illicit or prescription opioids. Diagnostic criteria were permitted to vary by study. Ideally, investigators would have applied accepted criteria for diagnosing OUD, such as that provided by the Diagnostic and Statistical

Manual of Mental Disorders (DSM) III, IV, or V.[15] However, we included studies that did not specify a diagnostic tool, instead relying on physician diagnosis or prior inclusion in a treatment program for OUD. All patient populations with OUD were eligible regardless of comorbidity. This included patients with chronic pain or concurrent substance use disorders. We did not consider studies in prison or pregnant populations.

3.2.3 Experimental Intervention

Receiving medication-assisted maintenance treatment, with or without initiation of therapy, in primary care. For the purpose of this review, we classified primary care as a singular setting, usually community based, where patients could receive care for their diagnosis of OUD, as well as for any other health conditions they may have. Primary care could be staffed by primary care physicians, nurse practitioners, or general internal medicine physicians and may or may not have the support of an interdisciplinary team. We included all trials offering OAT, regardless of the differences in additional resources available (e.g. counseling or multidisciplinary teams). However, we did not include trials in which there were substantial barriers to attendance in only one arm (e.g. patients needing to pay for their medications in one arm and not the other).

3.2.4 Comparison Intervention

Receiving medication-assisted treatment in an OUD-specialized setting. For the purpose of this review, we considered an OUD-specialized setting to be any setting that focuses on or has augmented services for management of opioid use disorder, with the assumption that at least some other health concerns are being managed elsewhere. These specialized settings could include publicly or privately funded facilities that staff a variety of health professionals,

including addiction specialists, nurses, pharmacists, psychiatrists, psychologists, and support services.

Types of Outcome Measures

3.2.5 Primary Outcomes

1. Treatment retention: we accepted retention as it is uniquely defined by each study, providing it adhered to a common definition such as retention in the program until the end of the study or compliance with the program protocol.
2. Abstinence from street opioids: we accepted abstinence as it is uniquely defined by each study, providing it adhered to a common definition such as abstinence via achieving a threshold number of negative urine opioid tests, a threshold number of negative urine tests for all drugs of misuse (including opioids), or via self-report. If urine screening measures of abstinence were available for both all drugs of misuse and opioids alone, we chose opioids alone for our measure of abstinence. If self-report and urine screening are available, we chose urine screening.
3. Major adverse events.
4. Withdrawals due to adverse events.

3.2.6 Secondary Outcomes

1. Quality of life on treatment: we accepted 'quality of life' as it is uniquely defined by each study, providing it adhered to a common definition. We combined this outcome in analysis only when it could be converted to a 0-to-10-point scale. This could include assessing various spheres of functioning and creating an overall global estimate (e.g. EQ-5D), or by assessing a particular domain considered to be relevant to OUD such as degree

of drug dependence (e.g. Leeds Dependence Questionnaire). To convert, for example, from a 30-point Leeds Dependence Questionnaire to our 10-point quality of life scale, we would multiply each mean and standard deviation by 10/30. Analysis would be by comparing the mean quality of life scores between groups at the latest time point such data were acquired.

2. Patient satisfaction: we accepted 'high satisfaction' as uniquely defined by each study, providing it adhered to a common definition such as meeting a threshold definition of high satisfaction on an interval scale. This could mean, for example, patients identifying themselves as 'very satisfied,' or their care as 'excellent.'
3. All-cause mortality.
4. Opioid-related mortality.
5. All-cause hospitalization or emergency department visit.
6. All-cause incarceration.
7. Minor adverse events.

Search Methods

3.2.7 Electronic Searches

We identified published, unpublished, and ongoing studies by searching the following databases from their inception:

1. Cochrane Drugs and Alcohol Group (CDAG) Specialized Register (most recent);
2. Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (most recent);
3. MEDLINE (Ovid) (1946 onwards);

4. Embase (Ovid) (January 1974 onwards);
5. PsycINFO (Ovid) (1800 onwards);
6. CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCOhost) (1982 onwards);
7. LILACS (Latin American and Caribbean Health Sciences Literature database) (1982 onwards);
8. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) via the Cochrane Register of Studies (CRS);
9. World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch).

The subject strategies for databases was modeled on the search strategy designed for MEDLINE in Appendix 1. Where appropriate, these were combined with subject strategy adaptations of the Highly Sensitive Search Strategy designed by Cochrane for identifying randomized controlled trials and controlled clinical trials (as described in Box 6.4.b of the *Cochrane Handbook for Systematic Reviews of Interventions*).[16]

3.2.8 Searching other Resources

We checked all references in selected studies to identify additional studies. We also contacted the authors of included studies to inquire as to other published or unpublished work.

Data Collection and Analysis

3.2.9 Selection of Studies

Two review authors independently screened the titles and abstracts of studies retrieved by the search for potential eligibility. We obtained the full-text reports for studies deemed potentially eligible, and both review authors appraised these to determine if they met the inclusion criteria of the review. Any disagreements at the full-text stage were resolved by consensus or by consulting a third review author.

3.2.10 Data Extraction and Management

Two review authors independently extracted data onto templates specifically designed for randomized controlled trials. One review author independently performed data entry into Review Manager 5 software, and a second review author checked the data entry for completeness and accuracy.[17]

We extracted the following data when available: descriptions of study participants (age, gender, health conditions, etc.), interventions, comparators, outcomes, study location, study design, funding source(s), and study time frame.

3.2.11 Assessment of Risk of Bias in Included Studies

Two review authors independently assessed the included studies for risk of bias using the Cochrane Risk of Bias tool.[18] The two-part tool addresses seven specific domains: sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessor (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other sources of bias. Initially, we described what is reported in each trial (part one). Then, we assigned a judgement related to the risk of bias for that entry, that is low, high, or unclear risk of bias. To make this judgement,

we utilized criteria as described by the *Cochrane Handbook for Systematic Reviews of Interventions*[18] adapted to the addiction field. See Supplement 3.2 for details.

We addressed the domains of sequence generation and allocation concealment (avoidance of selection bias) with a single entry for each study. We considered blinding of participants, healthcare providers, and outcome assessors (avoidance of performance bias and detection bias) separately for objective outcomes (e.g. dropout, use of substance of misuse measured by urine analysis, participants who relapsed at the end of follow-up, participants engaged in further treatments) and subjective outcomes (e.g. duration and severity of signs and symptoms of withdrawal, patient self-reported use of substance, side effects, social functioning as integration at school or at work, family relationship, etc.). We considered incomplete outcome data (avoidance of attrition bias) for all outcomes except for dropout from treatment, which is very often the primary outcome measure in trials on addiction.

3.2.12 Measures of treatment effect

We analysed dichotomous outcomes by calculating the risk ratio (RR) for each trial with the uncertainty around each estimate expressed as a 95% confidence interval (CI). We analysed continuous outcomes by calculating the mean difference (MD) with 95% CI when the studies use the same instrument for assessing the outcome. We used the standardized mean difference (SMD) when the studies use different instruments.

3.2.13 Unit of Analysis Issues

We expected all included studies to analyze their data at the same level as the randomization. If cluster-randomized trials with a participant-level analysis were found, such studies would need to account for clustering using an intra-cluster coefficient to be included in meta-analysis.

3.2.14 Dealing with Missing Data

For studies with missing data, we attempted to contact study authors to obtain the missing data. If participant-level data were available, and data elements are missing, we chose the method of imputing data that provides the most probable value when this can be calculated (e.g. choosing a value from an adjacent follow-up visit). When no such alternative existed, we imputed the value that is most conservative (e.g. assuming the worst outcome when data are missing).

3.2.15 Assessment of Heterogeneity

We report heterogeneity in two ways: first by reported I^2 statistic, and second by describing the differences in outcomes, interventions, and comparators within trials. We expected heterogeneity due to organization differences globally, therefore we utilized a random-effects model.

3.2.16 Assessment of Reporting Biases

Based on recommendations in the *Cochrane Handbook for Systematic Reviews of* Intervention,[19] if more than 10 studies are available for meta-analysis, a funnel plot is created to identify any potential sources of publication bias. Creating a funnel plot with fewer than 10 studies may lead to non-meaningful results that are due to chance.

3.2.17 Data Synthesis

When appropriate, we combined trial data using Review Manager 5.[17] In order to account for expected heterogeneity due to differences in primary and specialty care settings globally, we utilized a random-effects model.

3.2.18 Subgroup Analysis and Investigation of Heterogeneity

We utilized subgroup analysis to explore potential sources of heterogeneity, including:

1. Studies utilizing DSM criteria to identify eligible participants versus studies not using DSM criteria;
2. single-provider settings versus a team-based approach to treatment;
3. buprenorphine versus methadone maintenance therapy; and
4. studies that assessed transfer of care in patients stabilized in specialty care versus studies in which both primary and specialty care initiated opioid agonist therapy

3.2.19 Sensitivity Analysis

Where there were clear differences between trials in terms of bias, or where heterogeneity was substantial, we presented results both with and without the outlying trials.

3.3 RESULTS

3.3.1 Results of the Search

Electronic searching of nine comprehensive databases yielded a total of 1670 records. After removal of duplicates, 1018 unique titles were identified for title and abstract review. After dual review, 17 articles were pulled for full-text examination, with six meeting our inclusion criteria (Table 3-1).[20-25] The PRISMA flow diagram is available in Figure 3-1.

3.3.2 Included Studies

Six randomized controlled trials studying 493 (ranging from 22 to 221) patients with opioid use disorder were included in this review.

3.3.3 Excluded Studies

Of 17 studies identified for full-text review, 11 did not meet our inclusion criteria.[26-36] Reasons for exclusion included: wrong study design,[26,29,31-32,35] wrong intervention,[27,30,34] wrong

comparator,[36] and inability to retrieve article.[28,33] Details of the excluded studies are included in Table 3-4.

3.3.4 Patient Populations

Patients were on average 38 years old, primarily male (71%) and followed for a mean 46 weeks (ranging from 12-52 weeks). Participant enrollment varied widely between included studies. Three studies[20,23-34] enrolled patients not currently prescribed opioid agonist therapy, requiring initiation of treatment in either primary or specialty care. Alternatively, three studies[21-22,25] required patients to be stabilized for 6-12 months on opioid agonist therapy in one of the participating methadone maintenance programs in order to be enrolled in the study. Depending on the study, this meant that patients were required to be stabilized on opioid agonist therapy,[21-22,25] receiving take-home privileges,[22,25] and opioid-abstinent, validated through urine sample.[21-22] Additionally, one study required patients to provide verification of full-time employment.[22] These trials then randomized patients to continue maintenance treatment in specialty care or transferred maintenance to a primary care setting. Definitions of opioid use disorder were not well defined in most trials, with only two[23-24] identifying the use of the DSM criteria for patient eligibility. More detailed descriptions of included patient populations are available in Table 3-2.

3.3.5 Study Settings

Study setting was also highly variable between trials. Five of the included studies were conducted in the United States of America[21-25] and one was conducted in France.[20] Types of primary care physicians ranged from general internists,[21,23-24] infectious-disease trained physicians,[23] and "addictions" physicians[22] to more general descriptions of primary care physicians working in community settings.[20,25] Two studies[20,22] described a single provider

managing the care for patients randomized to primary care, while the remaining four studies utilized a team-based approach to treatment.[21,23-25]

3.3.6 Training and Resources in Individual Trials

Finally, training and resources were often provided to participating primary care providers, however type, frequency and amount of training varied between trials. In two trials, included primary care physicians had previous training or experience in caring for patients with opioid use disorder.[20,23] In Carrieri 2014, two ½ days of additional training were provided along with an in-service training for office staff and access to a 24-hour pager to consult specialists for any questions or concerns. Two trials reported buprenorphine induction and maintenance training for physicians[23] and an 8-hour training day and visit to the participating methadone maintenance program to observe practice.[25] Lastly, in three trials, the participating primary care setting was affiliated with or located near a specialty program.[20,22,24] A detailed description of training protocols provided by each trial is included in Table 3-3.

Outcomes

Outcomes reported included treatment retention, opioid abstinence, patient satisfaction and patient preference. Adverse events were rarely reported.

3.3.7 Retention in Treatment

Retention in treatment was reported by all six studies. At a mean 46 weeks, 80% of patients treated in primary care were retained in treatment, compared to 63% of patients in specialty care. While favouring primary care, this result was not statistically significant [Six RCTs, 493 patients; Risk Ratio (RR) 1.19 95% Cl 0.98, 1.45]. The meta-graph for overall treatment retention is available in Figure 3-4.

3.3.8 Opioid Abstinence

Five of the six included trials reported patient-level abstinence data. The author of the sixth trial was contacted and was not able to provide patient-level data.[22] The five included trials reported on illicit opioid use, however two trials combined opioid use with other drug use, including cocaine or benzodiazepines.[21,25] While the majority of trials required positive urine sampling as criteria for illicit drug use, one trial combined both urine sampling and self-report,[21] and one trial did not utilize urine samples but instead asked a validated question about opioid use during phone interviews.[20] At a mean 46 weeks, 55% of patients treated in primary care were opioid and/or drug abstinent compared to 34% treated in specialty care (five RCTs, 428 patients; RR 1.59 95% Cl 1.03, 2.46). The meta-graph for overall opioid abstinence is available in Figure 3-9.

3.3.9 Subgroup Analyses for Treatment Retention and Opioid Abstinence

Subgroup analyses conducted to determine the influence of type of opioid agonist therapy (buprenorphine versus methadone), criteria to determine opioid use disorder in participants (DSM criteria versus no criteria specified), type of primary care setting (single provider versus team-based settings), and definition of provision of treatment (transfer of stabilized patients to primary care versus initiation of opioid agonist therapy) did not find any effect on treatment retention or abstinence. Meta-graphs for all subgroups are available in Supplement 3-5, 3-6, 3-7, 3-8, 3-10, 3-11, 3-12, and 3-13.

Finally, a sensitivity analysis of fixed-effects for both treatment retention and opioid abstinence found similar results to the random-effects primary analysis. Meta-graphs are available in Supplement 3-3 and 3-4.

3.3.10 Major Adverse Events

Major adverse events were not reported in any of the trials. One patient with a history of suicide attempts deliberately overdosed on methadone, however the study did not specify which treatment setting the patient was randomized to.[20]

3.3.11 Quality of Life

Quality of life indicators were measured by two studies using the Short-Form-36 (SF-36) questionnaire[21] and the Addiction Severity Index.[21-22] Both studies found no difference between groups in any indicators. Finally, one trial found that 97% of patients treated in primary care and 81% of patients in specialty care initiated new work or social activities during the study period.[22]

3.3.12 Patient Satisfaction

Patient satisfaction was reported in three trials. Patients treated in primary care were very satisfied with treatment more often than those treated in specialty care (77% versus 38%; p=0.01).[21] Similarly, patients in primary care reported being more satisfied with the explanations regarding treatment they received in primary care compared to in specialty care.[20] Finally, patients in primary care reported a mean satisfaction score of 30.5 compared to 29.5 in specialty care at 52 weeks (Score 8-32, higher indicating greater satisfaction; no p-value given).[22]

3.3.13 All-Cause Mortality

All-cause mortality was reported by one trial.[23] In total, five patients died during the study period. One patient in the primary care intervention died of pre-existing end stage renal disease. Four patients in the specialty care (referred) treatment arm died of end stage renal disease (1 patient), pneumonia and sepsis (1 patient) and unknown causes (2 patients).

One trial reported on emergency department visits and hospitalizations and found no difference between treatment arms (35% primary care versus 36% specialty care; p=1.00).[23]

3.3.14 Minor Adverse Events

Occurrence of opioid withdrawal symptoms was reported by one trial, which found a decrease in symptoms over time for both treatment groups (p<0.001), however no difference between settings (p=0.6).[21] Adverse events that occurred in more than 20% of patients were reported by one trial, however they did not differentiate between treatment settings.[20] Common adverse events included: fatigue (49%), sleeping problems (48%), constipation (40%), shortness of breath (33%), muscle pain (32%), tingling (32%), decrease in appetite (31%), wheezing (31%), loss of sexual desire (31%), stomach pain (28%), headaches (28%), joint pain (23%), weight loss (20%), and blackouts (20%).

3.4 DISCUSSION

This systematic review evaluated patient-important outcomes in the management of opioid use disorder between two treatment settings: primary care and specialty care. Six randomized controlled trials met our inclusion criteria and were included in our review.

3.4.1 Summary of main results

The results of this review found a higher proportion of opioid abstinence, and greater patient satisfaction, for patients treated in primary care settings. Benefit was seen in primary care irrespective of if the provider was required to initiate opioid agonist therapy or provide maintenance treatment only. While not statistically significant, a trend in favour of primary care was also seen for treatment retention. Quality of life indicators reported in two trials were not statistically different between treatment settings. Adverse events were rarely reported with only

one trial reporting no statistical difference in the incidence of withdrawal symptoms between treatment settings.

3.4.2 Quality of the Evidence

The quality of evidence in the included trials was reduced due to the fact that in the majority of trials, many of the quality markers were not adequately described. For example, only one trial reported a published protocol[20] which we used to ensure that all a priori outcomes were accounted for. While the nature of the intervention and comparator made it impossible to allow for participant blinding, the majority of studies reported appropriate randomization sequence generation. Unfortunately, it was unclear in four trials if allocation sequence was properly concealed and unclear in three trials if outcome assessors were blind to treatment setting. If these indicators would have been met, our confidence in the study findings would have increased. Most trials did an adequate job of capturing reasons for discontinuation, with only one study not clearly reporting study drop-outs.[25] Publication bias could not be assessed with a funnel plot as only six trials were available for analysis. See Table 3-4 for details on the quality of evidence in each individual study. Additionally, for the Cochrane Risk of Bias Graph and Risk of Bias Summary see Figure 3-2 and Figure 3-3, respectively.

3.4.3 Overall completeness and applicability of evidence

While the included studies reported sufficient data to report on treatment retention and opioid abstinence, longer and larger studies may be required to further understand any differentials in adverse events or mortality between opioid use disorder management in primary versus specialty care.

Studies captured primary care in France and the U.S., however applicability to Canadian primary care settings may be limited due to the various definitions of primary care used among all studies. It could be argued that the trial conducted in France may be most applicable to Canadian primary care for a number of reasons.[20] First, European healthcare systems parallel the Canadian system more closely than the privatized U.S. system. Second, while the trial did require primary care physicians to have some experience or training in caring for patients with opioid use disorder, they utilized community family physicians rather than general internists or other types of physicians. Finally, the trial showed benefit for primary care when the intervention was delivered by a single provider. This suggests that family physicians, with the support of an allied health care team, may have similar success in our Canadian primary care setting. It is also important to note that the trial enrolled patients not currently prescribed methadone or requiring a switch from buprenorphine, therefore induction and maintenance of methadone treatment was managed successfully by primary care providers.

While the subgroup analysis comparing transfer of stabilized patients to primary care and initiation of opioid agonist therapy in primary care did not show a difference for both treatment retention and opioid abstinence, all of the studies excluded high-risk patients, including: pregnant women[20,23-24] those with co-dependence on alcohol or benzodiazepines,[20-24] psychiatric illnesses,[21,24-25] or patients who were homeless.[21,25] It is unclear if these patients can and should be managed in a primary care setting.

Our systematic review was, to our knowledge, the first to compare treatment of patients with opioid use disorder in primary and specialty care settings. Future research is essential to identify

the differences in patient-important outcomes in primary care settings more closely approximating those we have in our Canadian healthcare system. Further, larger trials of longer duration are required to identify important differences in infectious disease transmission, overdose, mortality and other outcomes critical to this patient population. Finally, trials including higher risk populations, including those with psychiatric conditions or co-dependence, are required to determine what treatment setting is suitable for an important subset of this population.

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Table 3-1: Characteristics of Included Studies

Author, Year	Sample Size	Age	Sex (M, F)	Geographic Location	Study Duration	Intervention	Comparator
Carrieri 2014	221 (195 treated)	32 (median)	164 M, 31 F	France	52 weeks	Primary care physician with experience and/or training in caring for patients with opioid use disorder; also required to be in the near vicinity to one of the participating specialty care physicians	Specialty care physicians working in a medical center that specializes in drug and alcohol dependence.
						Physicians from both treatment arms underwent one-day training to ensure methadone induction and maintenance was standardized between groups.	
Fiellin 2001	46	41 (mean)	30 M, 16 F	USA	26 weeks	Care was transferred to six primary care physicians (general internists). Patients attended the office weekly to take one observed dose of methadone and receive a 6-day supply of methadone. Monthly, patients met with the physician for 30 minutes to	Care continued at the narcotic treatment program. The program provided the standard set of services for patients, including access to a physician, drug and alcohol counselor, social worker and employment services. Patients were required to attend the program between

						discuss any concerns and patients provided a urine sample. Physicians were recruited through a survey of patients currently enrolled in the participating narcotic treatment program.	one and three times a week to take observed doses of methadone and receive take-home doses of methadone. Patients also attended group counseling weekly. Monthly, patients provided urine samples and attended individual counseling.
King 2006	92 (65 used)	44 (median)	38 M, 27 F	USA	52 weeks	Care was transferred to one of two primary care offices (primary care community health center or an addiction physician's private office). Patients attended the clinic once per month to take one observed dose of methadone, receive a 27-day supply of methadone, provided a urine sample and attend a 20-minute counseling session with their physician.	Care continued in one of two participating methadone maintenance treatment programs. Patients attended the clinic once per month to take one observed dose of methadone, receive a 27-day supply of methadone, provided a urine sample and attend a 20-minute counseling session with their physician.
						All patients in both treatment arms completed a random medication recall once monthly, to ensure they were being compliant with their methadone doses. During the recall, patients also provided a urine sample.	

						For patients providing a drug-positive urine sample or failing a medication recall, counseling and medication pick-up was increased, with primary care patients returning to their original clinic. Patients were required to pick up methadone five times per week and attend counseling sessions weekly.	
Lucas 2010	96 (93 treated)	46 (median)	67 M, 26 F	USA	52 weeks	Care was provided by a nurse with training as a substance abuse counselor who provided education to patients around buprenorphine induction. Trained primary care physicians started patients on buprenorphine and met with patients 4-6 weeks after induction or on an as needed basis. Patients picked up their buprenorphine in the clinic three times per week until stabilized (then switched to weekly pick-ups). Patients were required to attend the clinic for 10-40 minute "reporting visits", which included informal counseling, urine sampling,	Patients were enrolled in an "intensive case management program" that involved a case manager (nurse or social worker) making arrangements for referral to nearby opioid treatment programs. All patients were followed-up with to ensure they were attending the program as required.

						supervised buprenorphine doses and provision of take-home doses. These visits varied in frequency based on urine samples and other factors.	
O'Connor 1998	46	34 (mean)	32 M, 14 F	USA	12 weeks	Care was provided at the Central Medical Unit, a primary care setting run by general internists, nurse practitioners and physician associates. The settings treat patients with substance abuse disorders who are concurrently enrolled in programs affiliated with the Yale University Substance Abuse Treatment Unit. Patients were started on buprenorphine and received a 1-hour initial assessment, weekly 20-minute counseling sessions. Additionally, patients provided a weekly urine sample and attended 50-minute weekly group counseling sessions with a nurse practitioner.	Care was provided at the Legion Avenue Methadone Maintenance Program. Patients received the standard set of services, including an initial 2-3-hour assessment, a weekly 60-minute group counseling session and a monthly individual counseling session. Thrice weekly, patients were required to attend the clinic to receive their buprenorphine, provide urine samples and complete a self-reported questionnaire detailing symptoms.

Tuchman 2006	26 (22 treated)	42 (mean)	22 F, 0 M	USA	52 weeks	Care was transferred to four community physicians and one nurse practitioner. Patients were required to attend monthly visits to discuss any symptoms or medication concerns and to provide a urine sample. Patients were also assigned to one of five community pharmacists who observed methadone dosing and provided take-home doses. Patients also met with their care coordinator, a social worker, once monthly to discuss any concerns related to family, parenting, infections, education, housing, etc.	Care continued in the patient's original methadone maintenance clinic. Patients continued to see their regular healthcare providers and provided urine samples according to the clinic schedule (a minimum of 8 samples yearly).

Table 3-2: Description of Included Study Populations

Author, Year	Description of Included Patient Population
Carrieri 2014	All participating patients were "drug users" seeking treatment for their addiction. They were required to not currently be taking methadone (for at least one month) or to be switching to methadone from buprenorphine. Study did not mention the use of DSM Criteria. History of Drug Overdose: 12% (23/188) Use of Street Opioids: 72% (135/187) Proportion of patients switching from buprenorphine: 51% (99/195) Currently Employed: 51% (99/195)
Fiellin 2001	All patients were described as opioid-dependent and were eligible if they were receiving treatment at the participating narcotic treatment program for at least one year prior to study commencement. Beyond participation in the program, patients were required to be abstinent from opioids or cocaine for at least one year, as confirmed through urinalysis results, and anticipated to continue methadone maintenance treatment for at least six months. Study did not mention the use of DSM Criteria. History of IV Drug Use: 72% (33/46) Previous detoxification attempt: 91% (42/46) Current methadone maintenance duration: 4 years (mean) Currently Employed: 67% (31/46)
King 2006	All patients were required to be enrolled for at least twelve months in one of two participating methadone maintenance treatment programs: ATS at Hopkins Bayview or Man Alive Research. Verification was required of uninterrupted methadone treatment with no issues with medication recall, twelve months of opioid, cocaine, sedatives and other drug abstinence (via urinalysis) and full-time employment. Lifetime methadone treatment received: 14 years (mean)
Lucas 2010	All patients were currently being treated at the Johns Hopkins HIV Clinic, met DSM IV criteria for opioid dependence, had a positive urine for opioids and were seeking treatment for their dependence. Injection drug use in previous month: 60% (56/93) Years of opioid use: 19 years (median)

	Opioid use in past month: 30 days (median) Currently Employed: 30% (28/93)
O'Connor 1998	All patients were recruited from methadone wait-lists or through referrals to the study and met DSM III-R criteria for opioid dependence. Heroin use in the past 30 days: 30% (14/46) Intravenous drug use in the past 30 days: 57% (26/46) Previous methadone maintenance: 87% (40/46) Currently Employed: 48% (22/46)
Tuchman 2006	All patients were required to be enrolled in one of two participating methadone maintenance treatment programs with six months of continuous, stable methadone dosing and with privileges of at least two take-home doses of methadone weekly. Duration in methadone treatment: 5.3 years (mean)

Table 3-3: Description of Additional Training and/or Resources Provided to Primary Care

Author, Year	Resources/Training Provided to Primary Care Arm Only
Carrieri, 2014	All participating primary care physicians had experience and/or additional training in treatment of opioid use disorder. All participating primary care physicians were also in the near vicinity of a specialty care setting.
Fiellin, 2001	All participating primary care physicians were provided with a training manual, two ½ day training sessions and 24-hour support via pager. All office staff also received an in-service education session on opioid dependence, treatment strategies and the importance of incorporating treatment of opioid use disorder into primary care settings.
King, 2006	The two participating primary care settings were either in the near vicinity of or affiliated with one of the two participating specialty care centers.
Lucas, 2010	The primary care intervention was led by a licensed practical nurse who had additional training and experience as a substance abuse counselor. Additionally, the participating physicians (1 psychiatrist, 2 infectious disease physicians and 2 internal medicine physicians) are described in the study as "buprenorphine-prescribing" physicians, which the author confirmed required additional training.
O'Connor, 1998	The participating primary care clinic was affiliated with the Yale University Substance Abuse Unit and regularly cared for patients with substance dependence who attended treatment programs within the unit.
Tuchman, 2006	All participating primary care health providers (physicians, pharmacists and social worker) received 8 hours of training and a visit to the participating methadone maintenance treatment program to observe practice and methadone administration and dosing.

Table 3-4: Characteristics of Excluded Studies

Study	Reason for Exclusion	Description
Bevanda 2017	Wrong Study Design	Observational, cross-sectional design measuring demographic variables across various treatment settings
Doran 2004	Wrong Intervention	Used buprenorphine for a 5-day assisted withdrawal from heroin; not used as maintenance therapy.
Drucker 2000	Unable to Retrieve Article	Attempted to contact the author for publication, however, did not receive a response.
Fiellin 2002	Wrong Study Design	Contacted author who confirmed this was not a randomized controlled trial.
Gibson 2003	Wrong Intervention	Those allocated to primary care were required to pay $25 per week, whereas there was no cost for patients allocated to methadone maintenance treatment. This cost differential was part of our exclusion criteria.
Jones 2007	Wrong Study Design	Review article discussing the considerations of treating women with opioid dependence.
Keen 2004	Wrong Study Design	Study was published; however no results were posted in trial registry. Reached out to author, who has published seven studies from the included data in the trial registry, none of which are RCTs.
Ling 2001	Unable to Retrieve Article	This is a conference proceeding. The author was contacted for the full publication, however, did not respond.
Miotto 2012	Wrong Intervention	Although the study mentions primary care, they are referring specifically to primary care psychiatry.
Roux 2012	Wrong Study Design	This is the published protocol for one of our included studies, Carrieri 2014.

Watkins 2017	Wrong Comparator	The comparative intervention was not specialized care but rather a set of augmented services, including access to a care coordinator who encouraged patients to meet with a therapist to discuss treatment options.

Table 3-5: Risk of Bias in Individual Studies

Risk of Bias Domains (reported by individual studies)		
Study: Carrieri, 2014		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Described in the text: "Simple random sampling with no block control on randomization rate" was used.
Allocation concealment (selection bias)	Low Risk	Described in the text: "Randomization of patients was performed centrally by the study's methodology and data management center via a secured intranet site".
Blinding of participants and personnel (performance bias)	High Risk	Unable to blind participants and personnel due to the nature of the intervention.
Blinding of outcome assessment (detection bias)	Low Risk	Described in the text: "Information about patient randomization was confidentially stored and hidden from the study research team, except statisticians and the data manager, until the end of the last M12 interview, in December 2011".
Incomplete outcome data (attrition bias)	Low Risk	All data for ITT analysis of the study outcomes was provided.
Selective reporting (reporting bias)	Low Risk	The outcomes listed in the study's published protocol were consistent with final publication.
Other bias	Low Risk	No other obvious source of bias.
Study: Fiellin, 2001		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Described in the text: "Randomization and treatment allocation for all patients were determined using a computer-generated random-number table for an intended sample size of 60 patients, using a block size of 60".

Allocation concealment (selection bias)	Low Risk	Allocation concealment was maintained "by an investigator who had no information aside from the study identification number. Treatment allocation was communicated by this investigator to a separate investigator, not involved in assessment for eligibility or randomization, who notified each patient of his/her treatment assignment in a sequential manner".
Blinding of participants and personnel (performance bias)	High Risk	Unable to blind participants and personnel due to the nature of the intervention.
Blinding of outcome assessment (detection bias)	Unclear Risk	While it does mention that urine and hair toxicology testing was blinded in the trial, the assessors were not blind to urine collecting. No protocol was described in when urine collection was done during follow-up, therefore knowledge of the setting could have influenced the decision to obtain a urine.
Incomplete outcome data (attrition bias)	Low Risk	1 patient allocated to specialty care (1/25=4%) did not receive treatment in specialty care and was not included in the analysis.
Selective reporting (reporting bias)	Unclear Risk	Unable to locate published protocol or trial registry.
Other bias	Unclear Risk	All of the patients included in the trial were initially stable and being treated in specialty care. This already established relationship with specialty care, compared to an unknown relationship and new treatment environment in primary care, could have biased in favour of the specialty setting. The use of well-established methadone patients also led to a high clinical stability rate in both groups, which lessened the ability to show a difference between groups.
Study: King, 2006		
Bias	**Authors' Judgement**	**Support for Judgement**

Random sequence generation (selection bias)	Low Risk	Described in text: "Study patients were stratified on both self-report alcohol or drug use (past 30 days) and drug-positive urine samples over the past 2 years. Once stratified, patients were randomly assigned to one of three study conditions...".
Allocation concealment (selection bias)	Unclear Risk	Method of allocation concealment not described.
Blinding of participants and personnel (performance bias)	High Risk	Unable to blind participants and personnel due to the nature of the intervention.
Blinding of outcome assessment (detection bias)	Unclear Risk	Description of blinding of outcome assessors was not provided.
Incomplete outcome data (attrition bias)	Low Risk	6/98 participants who were randomized did not continue in the study, however 5 of these patients were in the routine care group which we did not use as a comparator. Only one of 32 participants randomized to office-based methadone maintenance treatment was not included.
Selective reporting (reporting bias)	Unclear Risk	Unable to locate published protocol or trial registry.
Other bias	Unclear Risk	Participants were recruited from two community methadone programs and were required to be stabilized on methadone for at least 12 months prior to being enrolled in the study. This already stable relationship in specialty care compared to an unknown relationship and new treatment environment in primary care, could be biased in favour of the specialty setting.
Study: Lucas, 2010		
Bias	**Authors' Judgement**	**Support for Judgement**

Random sequence generation (selection bias)	Low Risk	Described in text: "Using a statistical software package, we generated a random, non-stratified treatment allocation list before study inception, with block sizes that varied randomly between 2 and 10".
Allocation concealment (selection bias)	Unclear Risk	While the text describes that opaque envelopes were used to determine allocation of assignment, this was not completed at a centralized location. It is unclear if those interacting with the patients could have influenced allocation.
Blinding of participants and personnel (performance bias)	High Risk	Unable to blind participants and personnel due to the nature of the intervention.
Blinding of outcome assessment (detection bias)	Unclear Risk	Description of blinding of outcome assessors was not provided.
Incomplete outcome data (attrition bias)	Low Risk	2 of 48 (4%) patients allocated to primary care and 1 of 48 (2%) patients allocated to specialty care did not receive the intervention and were excluded from the study.
Selective reporting (reporting bias)	Unclear Risk	Unable to locate published protocol or trial registry.
Other bias	Low Risk	No other obvious source of bias.
Study: O'Connor, 1998		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	Low Risk	Statement given that patients were randomly assigned to each treatment arm.
Allocation concealment (selection bias)	Unclear Risk	Method of allocation concealment not described.
Blinding of participants and personnel (performance bias)	High Risk	Unable to blind participants and personnel due to the nature of the intervention.

Blinding of outcome assessment (detection bias)	Low Risk	Due to the fact that urine samples were processed by a third-party laboratory, it is unlikely that those analyzing the samples were aware of treatment allocation.
Incomplete outcome data (attrition bias)	Low Risk	All 46 patients who started the trial were accounted for in data analysis.
Selective reporting (reporting bias)	Unclear Risk	Unable to locate published protocol or trial registry.
Other bias	Low Risk	No other obvious source of bias.
Study: Tuchman, 2006		
Bias	**Authors' Judgement**	**Support for Judgement**
Random sequence generation (selection bias)	High Risk	The randomization process described in the trial is confusing and may imply that patients may have had some choice in their allocation. From the text: "Early in the enrollment period, it became evident that the sample size would be limited by constraints outside the control of the investigators. For that reason, the design was altered to allow women who had been originally randomized into the control arm to crossover into the experimental condition. The crossover was voluntary and resulted in the addition of two subjects to OBP/CPD"
Allocation concealment (selection bias)	Unclear Risk	Method of allocation concealment not described.
Blinding of participants and personnel (performance bias)	High Risk	Unable to blind participants and personnel due to the nature of the intervention.
Blinding of outcome assessment (detection bias)	Low Risk	The third-party laboratory that processed urine samples was likely unaware of the treatment allocation.

Incomplete outcome data (attrition bias)	Unclear Risk	The study used a per-protocol analysis and at least one participant in the control arm is unaccounted for.
Selective reporting (reporting bias)	Unclear Risk	Unable to locate published protocol or trial registry.
Other bias	Unclear Risk	Participants were recruited from two community methadone programs and were required to be stabilized on methadone for at least 6 months prior to being enrolled in the study. This already stable relationship in specialty care compared to an unknown relationship and new treatment environment in primary care, could be biased in favour of the specialty setting.

Figure 3-1: PRISMA Flow Diagram

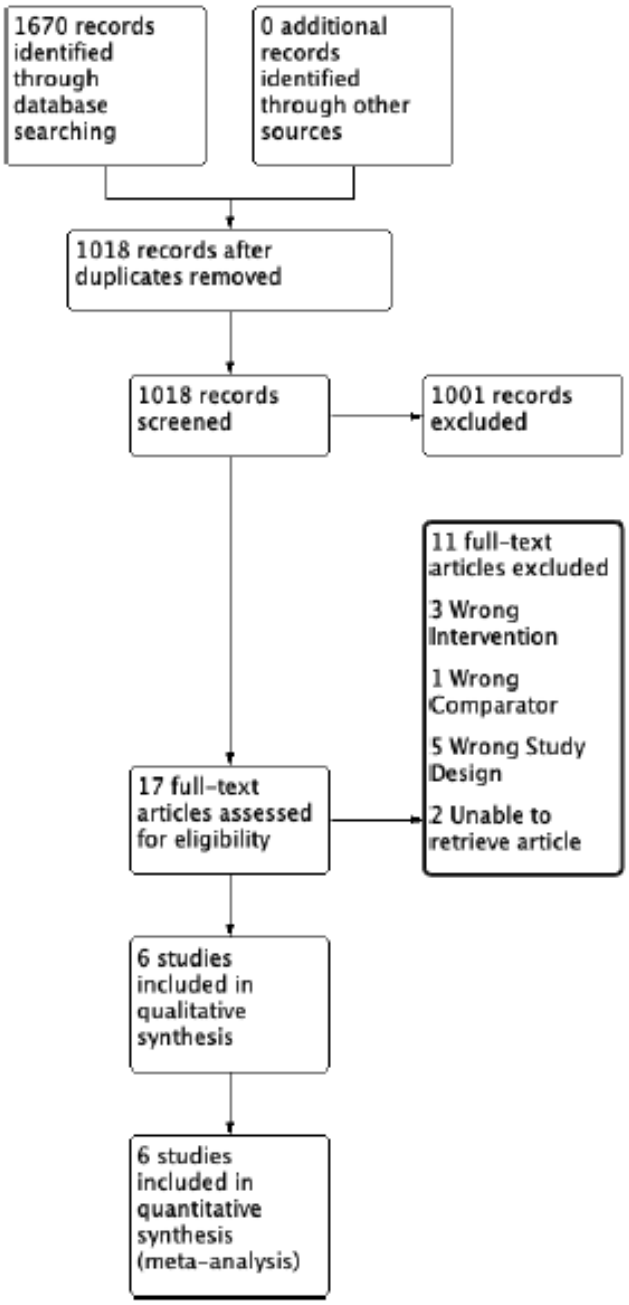


Figure 3-2: Cochrane Risk of Bias Graph

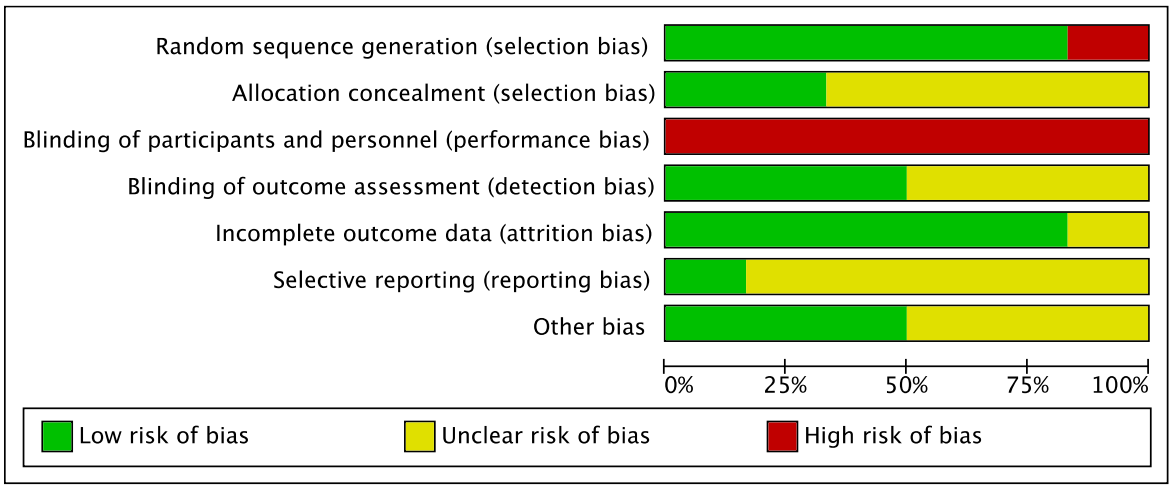


Figure 3-3: Cochrane Risk of Bias Summary

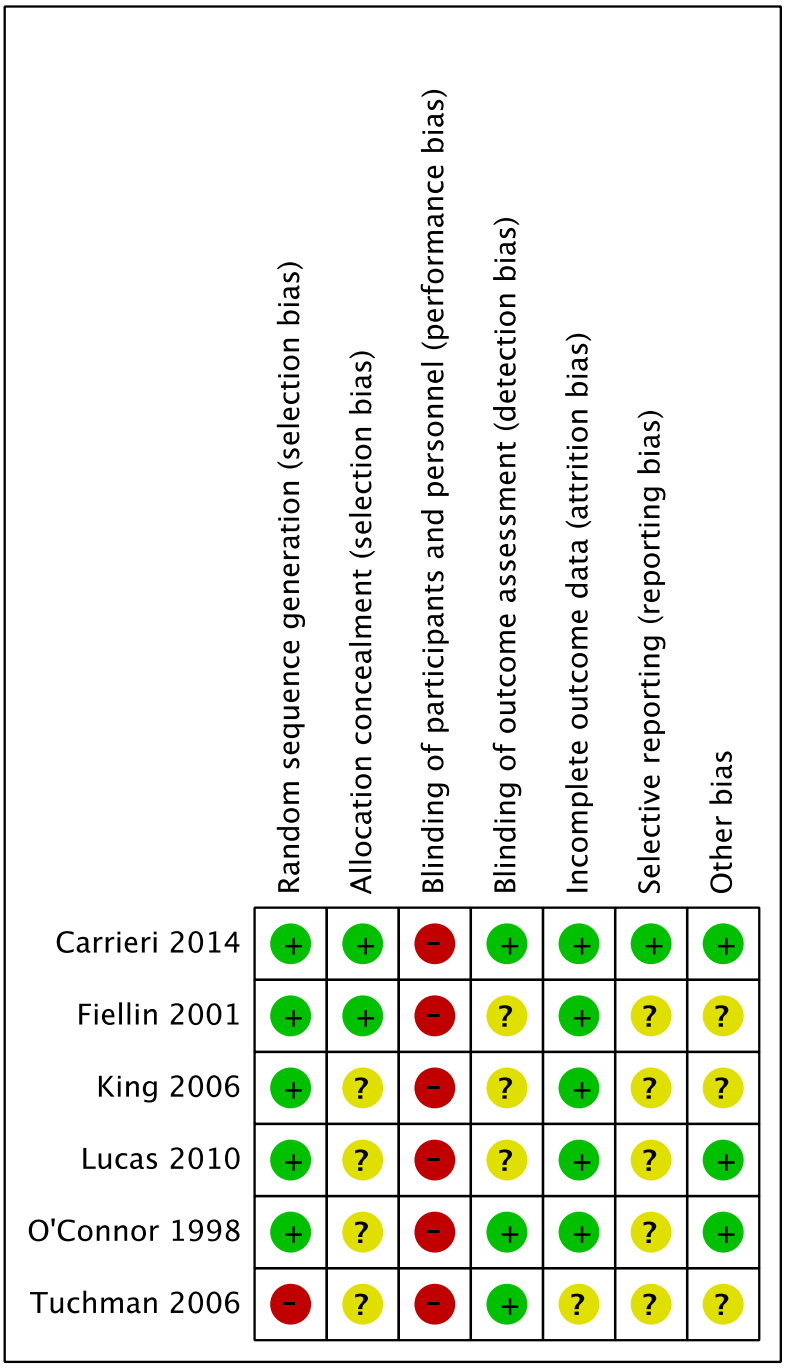


Figure 3-4: Primary versus specialty care; Outcome: Overall treatment retention

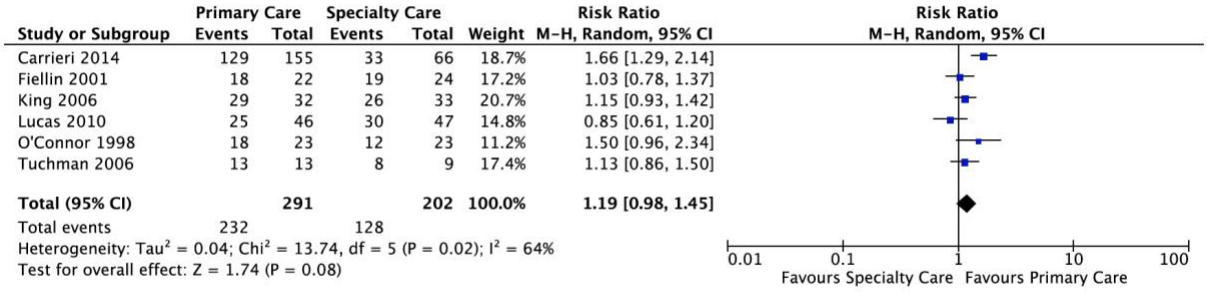


Figure 3-5: Primary versus specialty care; Subgroup analysis: Treatment retention, analyzed by primary care setting (single provider versus team-based care)

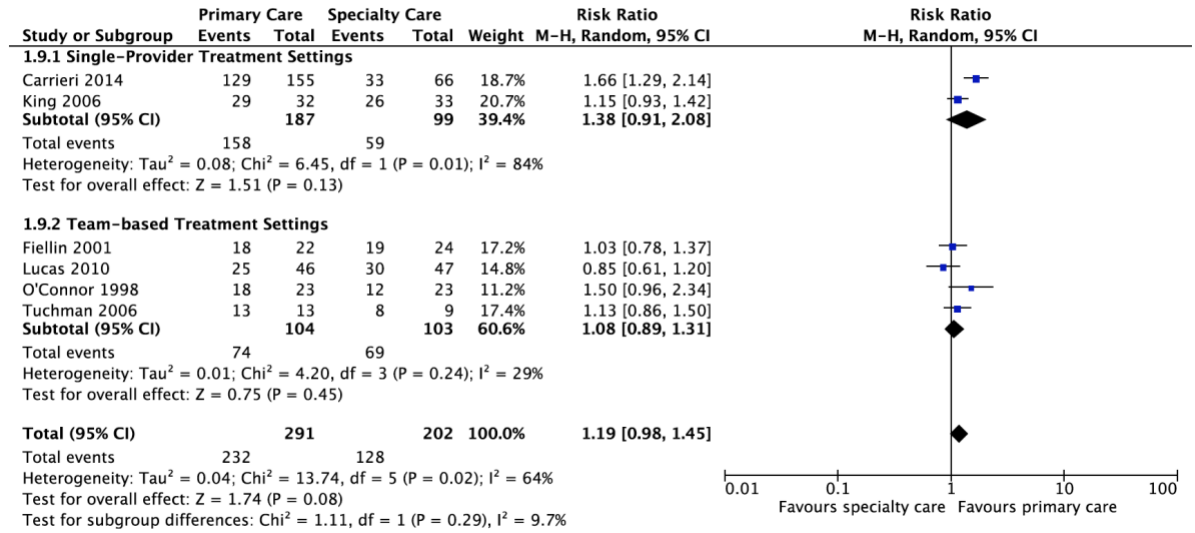


Figure 3-6: Primary versus specialty care; Subgroup analysis: Treatment retention, analyzed by type of opioid agonist therapy (buprenorphine versus methadone).

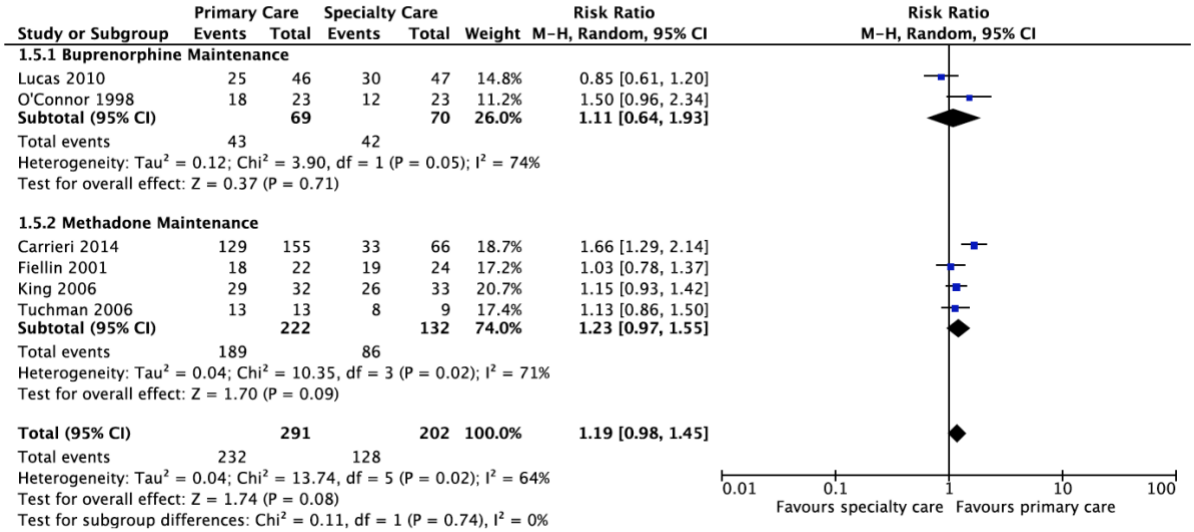


Figure 3-7: Primary versus specialty care; Subgroup analysis: Treatment retention, analyzed by definition of provision of treatment (transfer of stabilized patients to primary care versus initiation of opioid agonist therapy)

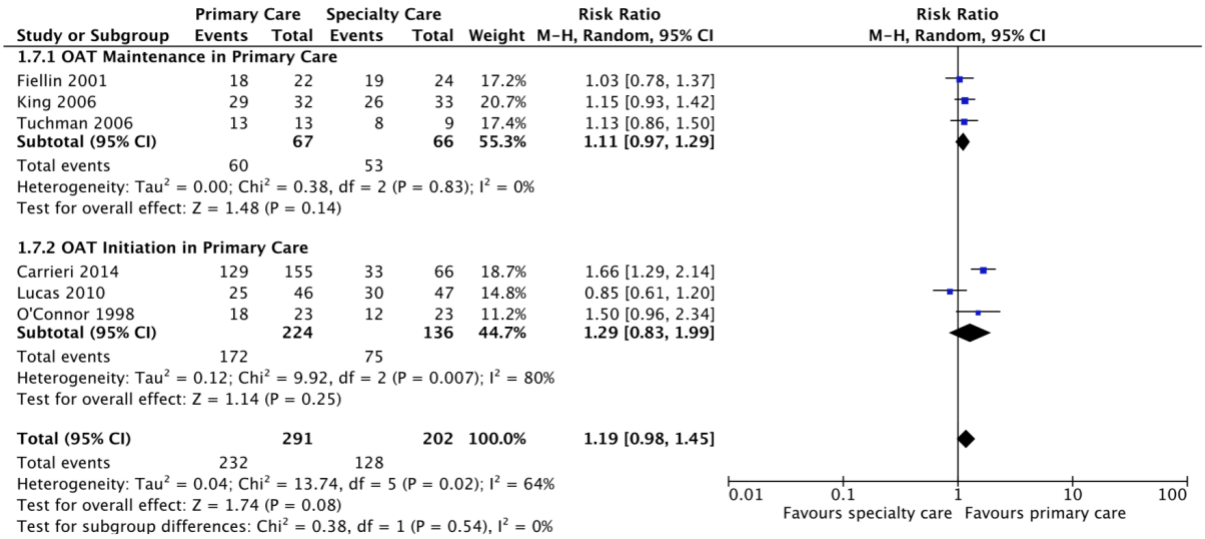


Figure 3-8: Primary versus specialty care; Subgroup analysis: Treatment retention, analyzed by utilization of DSM Criteria (studies that used DSM to identify patients versus those who did not)

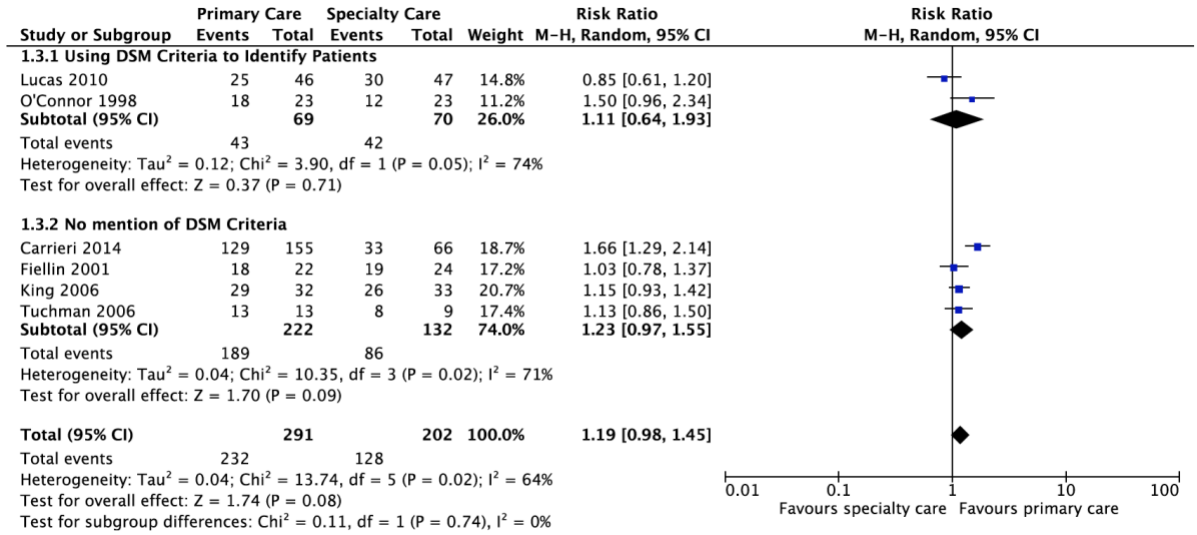


Figure 3-9: Primary versus specialty care; Outcome: Overall opioid abstinence

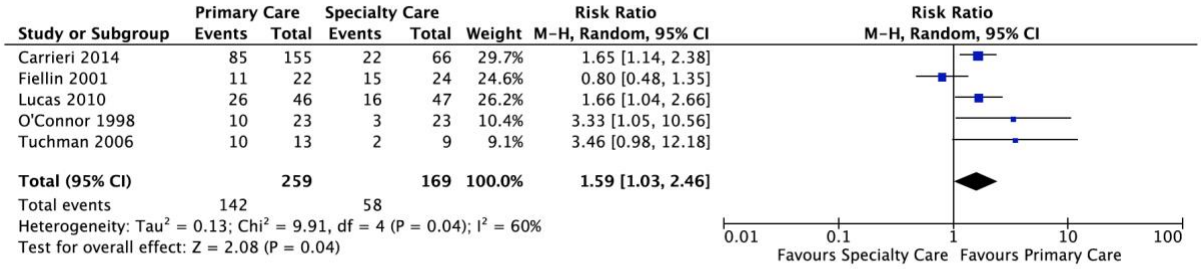


Figure 3-10: Primary versus specialty care; Subgroup analysis: Opioid abstinence, analyzed by primary care setting (single provider versus team-based care)

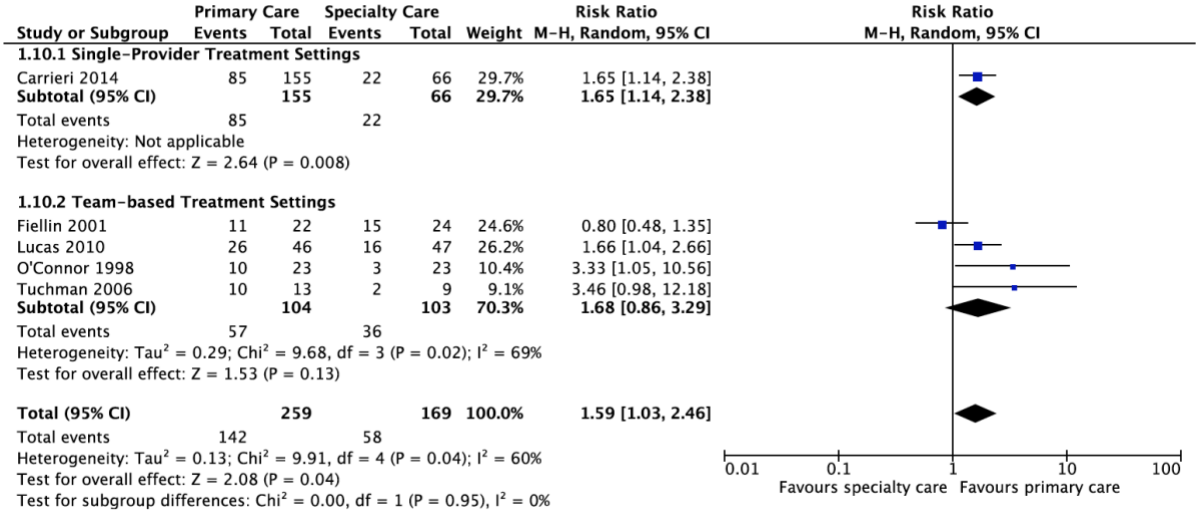


Figure 3-11: Primary versus specialty care; Subgroup analysis: Opioid abstinence, analyzed by type of opioid agonist therapy (buprenorphine versus methadone)

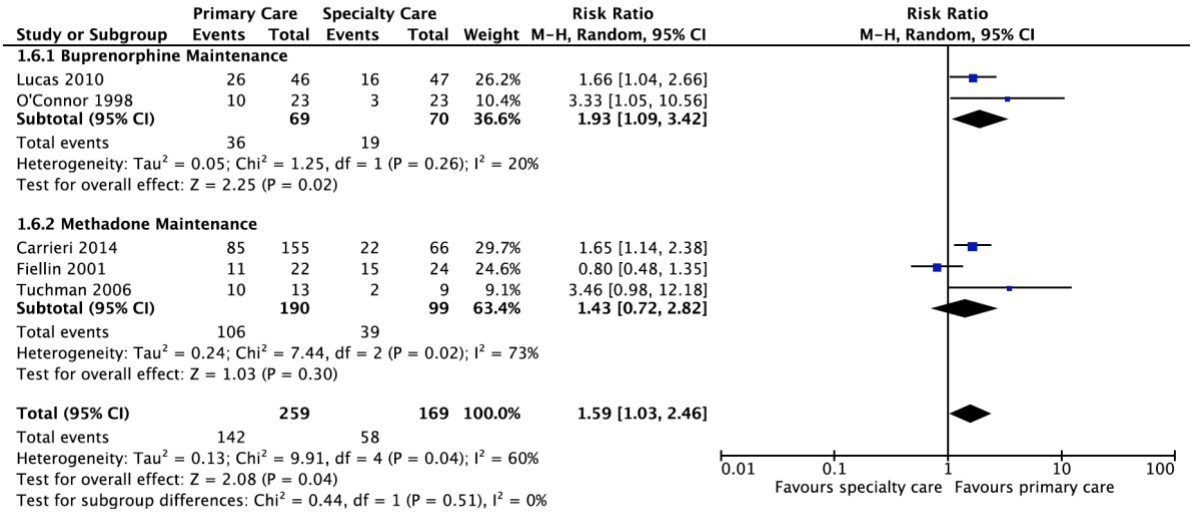


Figure 3-12: Primary versus specialty care; Subgroup analysis: Opioid abstinence, analyzed by definition of provision of treatment (transfer of stabilized patients to primary care versus initiation of opioid agonist therapy)

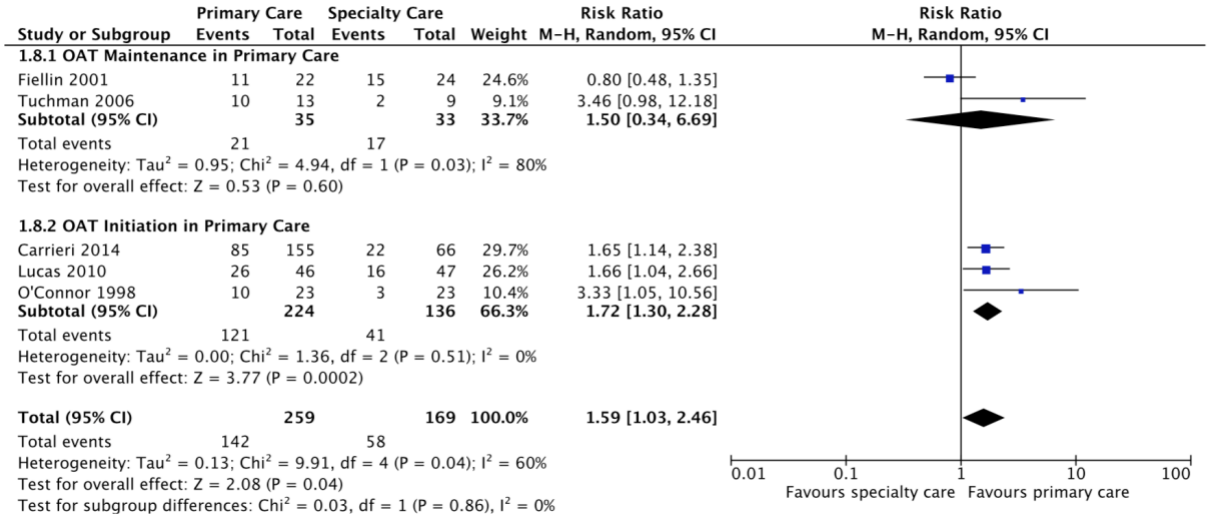
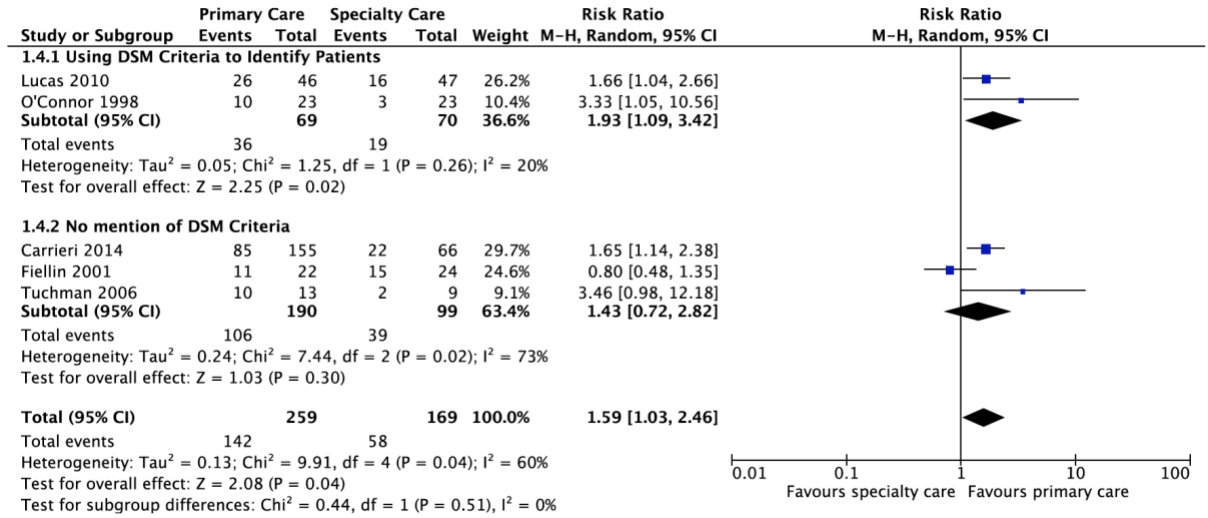


Figure 3-13: Primary versus specialty care; Subgroup analysis: Opioid abstinence, analyzed by utilization of DSM Criteria (studies that used DSM to identify patients versus those who did not)



Supplement 3-1: Cochrane Search Strategy

Cochrane Drugs and Alcohol Group (CDAG) Specialized Register via Cochrane Register of Studies (CRS) on July 13, 2020

#1 (opiat* or opioid* or heroin* or morphin* or morfin* or narcot*) AND INREGISTER

#2 ((substitut* or maint*) NEAR (treatment or therapy)) AND INREGISTER

#3 Methadone or Buprenorphine AND INREGISTER

#4 (OAT or OST or MMT or BMT) AND INREGISTER

#5 #2 OR #3 OR #4

#6 #1 AND #5

#7 MESH DESCRIPTOR General Practice EXPLODE ALL AND INREGISTER

#8 MESH DESCRIPTOR Primary Health Care EXPLODE ALL AND INREGISTER

#9 MESH DESCRIPTOR Community Health Services EXPLODE ALL AND INREGISTER

#10 MESH DESCRIPTOR Physicians, Primary Care EXPLODE ALL AND INREGISTER

#11 MESH DESCRIPTOR Physicians, Family EXPLODE ALL AND INREGISTER

#12 MESH DESCRIPTOR General Practitioners EXPLODE ALL AND INREGISTER

#13 ((general NEXT pract*) or (family NEXT pract*) or GP or physician*) AND INREGISTER

#14 ((family or community or practice*) NEXT (medic* or doctor* or physician* or health* or nurs*)) AND INREGISTER

#15 (primary NEAR2 care) AND INREGISTER

#16 (shared NEXT care) AND INREGISTER

#17 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16

#18 #17 AND #6

CENTRAL via CRS on July 13, 2020

#1 MESH DESCRIPTOR Opioid-Related Disorders EXPLODE ALL AND CENTRAL:TARGET

#2 MESH DESCRIPTOR Substance Abuse, Intravenous EXPLODE ALL AND CENTRAL:TARGET

#3 (((((opiat* or opioid* or heroin* or morphin* or morfin* or narcot*) and (use* or abus* or misuse* or addict* or depend*))):TI):AB):KY AND CENTRAL:TARGET

#4 ((((((drug* or substance) and (abus* or misuse* or addict* or depend* or disorder*))):TI):AB):AB):KY AND CENTRAL:TARGET
#5 #1 OR #2 OR #3 OR #4
#6 MESH DESCRIPTOR Opiate Substitution Treatment EXPLODE ALL AND CENTRAL:TARGET
#7 MESH DESCRIPTOR Methadone EXPLODE ALL AND CENTRAL:TARGET
#8 MESH DESCRIPTOR Buprenorphine EXPLODE ALL AND CENTRAL:TARGET
#9 ((substitut* or maint*) NEAR (treatment or therapy)) AND CENTRAL:TARGET
#10 ((OAT or OST or MMT or BMT):TI):AB AND CENTRAL:TARGET
#11 #6 OR #7 OR #8 OR #9 OR #10
#12 #11 AND #5
#13 MESH DESCRIPTOR General Practice EXPLODE ALL AND CENTRAL:TARGET
#14 MESH DESCRIPTOR Primary Health Care EXPLODE ALL AND CENTRAL:TARGET
#15 MESH DESCRIPTOR Community Health Services EXPLODE ALL AND CENTRAL:TARGET
#16 MESH DESCRIPTOR Physicians, Primary Care EXPLODE ALL AND CENTRAL:TARGET
#17 MESH DESCRIPTOR Physicians, Family EXPLODE ALL AND CENTRAL:TARGET
#18 MESH DESCRIPTOR General Practitioners EXPLODE ALL AND CENTRAL:TARGET
#19 (((((general NEXT pract*) or (family NEXT pract*) or GP or physician*)):TI):AB):KY AND CENTRAL:TARGET
#20 ((family or community or practice*) NEXT (medic* or doctor* or physician* or health* or nurs*)) AND CENTRAL:TARGET
#21 (primary NEAR2 care) AND CENTRAL:TARGET
#22 (shared NEXT care) AND CENTRAL:TARGET
#23 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#24 #23 AND #12

Database: Ovid MEDLINE(R) ALL <1946 to July 13, 2020>

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1 exp Opioid-Related Disorders/ (26548)

2 Substance Abuse,Intravenous/ (15153)

3 ((opiat$ or opioid$ or heroin$ or morphin$ or morfin$ or narcot$) adj3 (use$ or abus$ or misuse$ or addict$ or depend$)).tw. (42376)

4 ((drug* or substance) adj3 (abus$ or misuse$ or addict$ or depend$ or disorder$)).tw. (102416)

5 1 or 2 or 3 or 4 (156344)

6 Opiate Substitution Treatment/ (3011)

7 methadone/ (12304)

8 buprenorphine/ (5203)

9 (((substitut* or maint*) adj2 (treatment or therapy)) or methadone or buprenorphine).tw. (47876)

10 (OAT or OST or MMT or BMT).ti,ab. (23483)

11 6 or 7 or 8 or 9 or 10 (73444)

12 5 and 11 (14912)

13 exp General Practice/ (74927)

14 Primary Health Care/ (77402)

15 Community Health Services/ (31604)

16 Physicians, Primary Care/ or Physicians, Family/ (19727)

17 General Practitioners/ (7876)

18 (general pract$ or family pract$ or GP or physician$).tw. (494378)

19 ((family or community or practice$) adj (medic$ or doctor$ or physician$ or health$ or nurs$)).tw. (74629)

20 (primary adj2 care).tw. (134431)

21 shared care.tw. (1304)

22 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (691180)

23 12 and 22 (1491)

24 randomized controlled trial.pt. (509419)

25 controlled clinical trial.pt. (93751)

26 random*.ab. (1111177)

27 placebo.ab. (209333)

28 clinical trials as topic.sh. (192041)

29 random allocation.sh. (103176)

30 trial.ti. (221554)

31 24 or 25 or 26 or 27 or 28 or 29 or 30 (1611756)

32 exp animals/ not humans.sh. (4716916)

33 31 not 32 (1448731)

34 23 and 33 (180)

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Database: Embase <1974 to 2020 July 13>

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1 exp opiate addiction/ (19965)

2 intravenous drug abuse/ (10211)

3 ((opiat$ or opioid$ or heroin$ or morphin$ or morfin$ or narcot$) adj3 (use$ or abus$ or misuse$ or addict$ or depend$)).tw. (59775)

4 ((drug* or substance) adj3 (abus$ or misuse$ or addict$ or depend$ or disorder$)).tw. (136261)

5 1 or 2 or 3 or 4 (198510)

6 Opiate Substitution Treatment/ (2347)

7 methadone/ (31564)

8 buprenorphine/ (17940)

9 (((substitut* or maint*) adj2 (treatment or therapy)) or methadone or buprenorphine).tw. (73826)

10 (OAT or OST or MMT or BMT).ti,ab. (32349)

11 6 or 7 or 8 or 9 or 10 (124629)

12 5 and 11 (22277)

13 exp General Practice/ (77570)

14 exp primary health care/ (169118)

15 exp community care/ (115320)

16 exp general practitioner/ (98452)

17 (general pract$ or family pract$ or GP or physician$).tw. (680391)

18 ((family or community or practice$) adj (medic$ or doctor$ or physician$ or health$ or nurs$)).tw. (90307)

19 (primary adj2 care).tw. (178834)

20 13 or 14 or 15 or 16 or 17 or 18 or 19 (1022909)

21 12 and 20 (2761)

22 Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/ (2055522)

23 (((clinical or control or controlled) adj (study or trial)) or ((single or double or triple) adj (blind$3 or mask$3)) or (random$ adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or (crossover adj (design or study or trial)) or placebo or placebos).ti,ab. (1101218)

24 22 or 23 (2488243)

25 21 and 24 (432)

26 from 25 keep 1-432 (432)

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Database: APA PsycInfo <1806 to July Week 1 2020>

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1 exp "Opioid Use Disorder"/ (3388)

2 ((opiat$ or opioid$ or heroin$ or morphin$ or morfin$ or narcot$) adj3 (use$ or abus$ or misuse$ or addict$ or depend$)).tw. (19416)

3 ((drug* or substance) adj3 (abus$ or misuse$ or addict$ or depend$ or disorder$)).tw. (91303)

4 exp Intravenous Drug Usage/ (4092)

5 1 or 2 or 3 or 4 (107140)

6 methadone/ or methadone maintenance/ (5156)

7 exp Buprenorphine/ (1851)

8 (((substitut* or maint*) adj2 (treatment or therapy)) or methadone or buprenorphine).tw. (14963)

9 (OAT or OST or MMT or BMT).ti,ab. (2184)

10 6 or 7 or 8 or 9 (16082)

11 5 and 10 (7619)

12 exp Primary Health Care/ or exp General Practitioners/ (23063)

13 exp General Practitioners/ (5861)

14 (general pract$ or family pract$ or GP or physician$).tw. (79727)

15 ((family or community or practice$) adj (medic$ or doctor$ or physician$ or health$ or nurs$)).tw. (19419)

16 (primary adj2 care).tw. (35229)

17 shared care.tw. (361)

18 12 or 13 or 14 or 15 or 16 or 17 (117838)

19 11 and 18 (731)

20 exp Clinical Trials/ (12304)

21 (random* or (clinical adj3 trial*) or (reserch adj3 design*) or (evaluat adj3 stud*) or (prospective* adj3 stud*)).tw. (253120)

22 ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).tw. (26413)

23 20 or 21 or 22 (263501)

24 19 and 23 (107)

25 from 24 keep 1-107 (107)

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LILACS on July 15, 2020 (212 records)

(tw:((opiat* OR opioid* OR heroin* OR morphin* OR morfin* OR narcot*))) AND (tw:((abus* OR addict* OR depend*))) AND (tw:((“Opioid Substitution” OR OST OR OAT OR MMT OR BMT methadone OR buprenorphine OR “maintenance treatment” OR “maintenance therapy”))) AND (tw:((“Primary Health Care” OR “Primary Care” OR “shared care”))) AND (tw:((randomised OR randomized OR randomisation OR randomization OR trial OR placebo OR blind OR "phase 3" OR "phase III")))

CINAHL via EBSCOhost (343 records)

S34 S19 AND S33

S33 S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32

S32 TX rct

S31 (MH "Placebos")

S30 (MH "Quantitative Studies")

S29 (MH "Random Assignment")

S28 (MH "Clinical Trials+")

S27 TX versus OR vs

S26 TX phase and TX (three OR III)

S25TX "control group*"

S24 TX "treatment arm"

S23 TX (blind* OR mask*) and TX (single OR double OR triple OR treble)

S22 TX trial and TX (control* OR comparative)

S21 TX "cross over"

S20 TX random* OR factorial* OR placebo* OR assign* OR allocat* OR crossover*

S19 S10 AND S18

S18 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17

S17 AB((family OR community OR practice*) N2 (medic* OR doctor* OR physician* OR health* OR nurs*))

S16 TI((family OR community OR practice*) N2 (medic* OR doctor* OR physician* OR health* OR nurs*))

S15 TI(general N2 pract*) OR TI(family N2 pract*) OR TI(GP OR physician*)

S14 (MH "Physicians, Family")

S13 (MH "Community Health Services+") OR (MH "Shared Services, Health Care")

S12 (MH "Primary Health Care")

S11 (MH "Family Practice")

S10 S3 AND S9

S9 S4 OR S5 OR S6 OR S7 OR S8

S8 TI(methadone OR buprenorphine)OR AB(methadone OR buprenorphine)

S7 TI(OAT OR OST OR MMT OR BMT) OR AB(OAT OR OST OR MMT OR BMT)

S6 TI((substitut* OR maint*) N2 (treatment OR therapy)) OR AB((substitut* OR maint*) N2 (treatment OR therapy))

S5 (MH "Buprenorphine")

S4 (MH "Methadone")

S3 S1 OR S2

S2 TX((opiat* OR opioid* OR heroin* OR narcot*) N3 (abus* OR misuse* OR addict* OR depend*))

S1 (MH "Substance Abuse, Intravenous")

Supplement 3-2: Cochrane Risk of Bias Domains

Item	Judgement	Description
1. Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization.
	High risk	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention.
	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk
2. Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
	High risk	Investigators enrolling participants could possibly have foreseen assignments because one of the following methods was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear risk	Insufficient information to permit judgement of low or high risk. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definitive judgement.

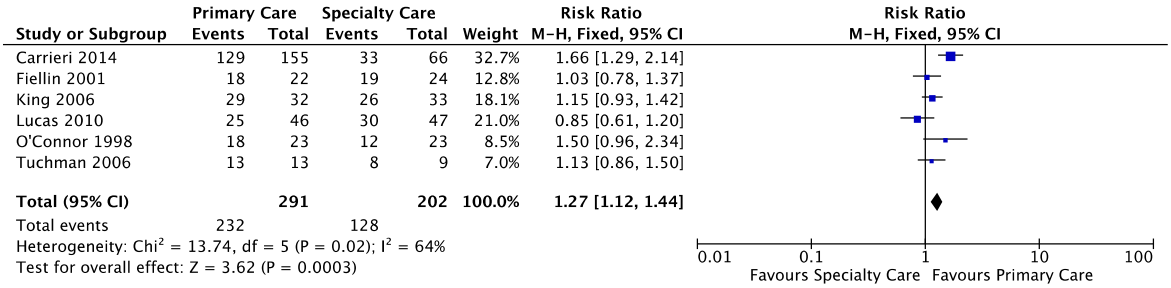
3. Blinding of participants and providers (performance bias) Objective outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to have been influenced by lack of blinding; blinding of participants and key study personnel ensured, and it is unlikely that the blinding could have been broken.
	High risk	No blinding or incomplete blinding, and the outcome is likely to have been influenced by lack of blinding; blinding of key study participants and personnel was attempted, but it is likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk
4. Blinding of participants and providers (performance bias) Subjective outcomes	Low risk	Blinding of participants and providers ensured and it is unlikely that the blinding could have been broken.
	High risk	No blinding or incomplete blinding, and the outcome is likely to have been influenced by lack of blinding; blinding of key study participants and personnel was attempted, but it is likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk
5. Blinding of outcome assessor (detection bias) Objective outcomes	low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to have been influenced by lack of blinding; blinding of outcome assessment ensured, and it is unlikely that the blinding could have been broken.
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to have been influenced by lack of blinding; blinding of outcome assessment, but it is likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

	Unclear risk	Insufficient information to permit judgement of low or high risk
6.Blinding of outcome assessor (detection bias) Subjective outcomes	Low risk	Blinding of outcome assessment ensured, and it is unlikely that the blinding could have been broken.
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to have been influenced by lack of blinding; blinding of outcome assessment, but it is likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk
7. Incomplete outcome data (attrition bias) For all outcomes except retention in treatment or dropout	Low risk	• No missing outcome data. • Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias). • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups. • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate. • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size. • Missing data have been imputed using appropriate methods. • All randomised participants are reported/analyzed in the group to which they were allocated by randomisation irrespective of non-compliance and co-interventions (intention-to-treat).

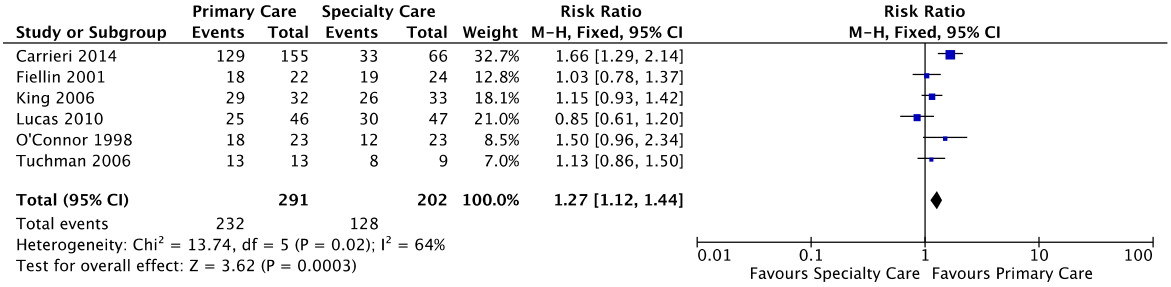
	High risk	• Reasons for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups. • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate. • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size. • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
	Unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of dropouts not reported for each group)
8. Selective reporting (reporting bias)	Low risk	The study protocol is available, and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way; the study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).
	High risk	Not all of the study's prespecified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include

		results for a key outcome that would be expected to have been reported for such a study.
	Unclear risk	Insufficient information to permit judgement of low or high risk

Supplement 3-3: Primary versus specialty care; Sensitivity Analysis: Treatment retention with fixed effects



Supplement 3-4: Primary versus specialty care; Sensitivity Analysis. Opioid abstinence with fixed effects



4 CHAPTER 4: SUMMARY

4.1 OVERVIEW OF RESEARCH AND OBJECTIVES

In 2017, 115,000 people died from an opioid-related overdose.[1] In Canada, 11 opioid-related deaths and 13 opioid-related hospitalizations occur every day.[2] Guidelines recommend opioid agonist therapy as first line treatment for patients with opioid use disorder, however obtaining treatment in specialty care settings can be challenging, owing to long wait-times, lack of transportation, and associated stigma.[3]

While traditionally managed in specialty care, primary care is well accustomed to caring for highly complex cases, with many primary care patients living with numerous comorbid health conditions.[4] Further, over 85% of Canadians already have an established therapeutic relationship with a primary healthcare provider.[5] Finally, having access to a single primary care provider or primary healthcare team for health-related concerns has been shown to improve health and decrease emergency department visits and hospitalizations.[6-10] It is possible that primary care offers a unique solution to the challenges faced by specialty care settings, by providing a convenient location with a familiar healthcare provider that patients can access for management of their opioid use disorder.

The objective of this dissertation was to determine if differences exist in patient-important outcomes between treatment of opioid use disorder in primary care and specialty care settings. If primary care was found to provide equivalent or superior care, it would support primary care as an additional option for patients seeking treatment for their opioid use disorder. Dissemination of these findings was done so in a systematic review and a clinical tool, Tools for Practice.

4.2 SUMMARY OF FINDINGS

Findings from my systematic review identified a higher proportion of opioid-abstinence and patient satisfaction in patients with opioid use disorder who were treated in primary care. While not statistically significant, 80% of patients were retained in treatment while in primary care, compared to 63% of patients treated in specialty care. Adverse events were underreported, however no difference in withdrawal symptoms, emergency department visits or hospitalizations were found between treatment settings.

This evidence suggests that primary care is equipped to provide equivalent or superior care for patients with opioid use disorder, when compared to more traditional specialized treatment settings. Benefit was seen in primary care regardless of whether the primary care provider was required to initiate opioid agonist therapy or provide maintenance treatment alone. The caveat to this evidence, is ensuring proper training and support to primary care settings. All included studies incorporated some aspect of support for primary care, including additional training for physicians and staff, located near a specialty care setting or having an affiliation with a specialty care setting.

4.3 IMPLICATIONS FOR PRACTICE

The results of this review support the provision of opioid use disorder management within primary care settings. Effectively implementing these changes, however, will require support from both primary care and specialized settings as well as the healthcare system as a whole.

In order to adequately adapt these practices in their offices, primary care physicians need to feel confident that they can safely initiate and maintain patients on opioid agonist therapy. To do this, specialty care settings should work with primary care providers to determine which patients can

be safely managed in primary care, while accepting those who may require additional support. The healthcare system needs to recognize the training and support that is required to implement opioid use disorder treatment in primary care settings and ensure that they are readily accessible to primary care providers. Training and support systems should be structured around the competing demands that primary care physicians face in their practices. This could be accomplished by providing incentives for completion of training, offering training online or on evenings and weekends, having a primary care champion who works within a practice to support other physicians or by making supports readily available to physicians (e.g., a telephone help line).

4.4 IMPLICATIONS FOR FUTURE RESEARCH

As stated above, an important issue with the current evidence is the lack of generalizability in the Canadian healthcare system. While treating patients with opioid use disorder in Canadian primary care settings is feasible with the proper support and training, it is imperative that future studies are conducted within Canada or in jurisdictions with similar healthcare systems, ideally publicly funded and designed / led by family physicians. Future trials in the Canadian context could consider investigating the concept of the patient's medical home, a model characterized by providing accessible, comprehensive team-based care to primary care patients.[11]

Secondly, future research should be conducted to include high-risk patients with opioid use disorder, specifically patients with co-dependence on other substances (e.g., alcohol or benzodiazepines), patients with psychiatric comorbidities or patients who are unemployed, homeless or facing other challenges in their personal lives. These patients represent a significant

portion of those with opioid use disorder. Canadian research has suggested that adults with substance use disorders are three times more likely to have a co-existing mental health condition.[12] In the U.S., over 40% of patients with a substance use disorder have symptoms of depression or anxiety.[13] Further, individuals who are unemployed, have a low income or who have limited education are at highest risk for hospitalization due to opioid poisoning.[14] Finally, history of substance use disorder, incidence of mental health disorders and concurrent prescription of psychiatric medications have been identified as factors associated with higher risk of opioid misuse and dependence.[15] It is imperative that research is conducted that includes these higher risk populations to determine the appropriate treatment setting for initiation of opioid agonist therapy and continued opioid use disorder management.

Finally, to further consider treatment of opioid use disorder within a Canadian primary care context, research should include representation of our Aboriginal population. This population represents over 1.6 million Canadians and is the fastest growing population in Canada, increasing by 43% between 2006 and 2016.[16] Evidence suggests a 5.6 times greater likelihood of hospitalization due to opioid poisoning in First Nations peoples living on reserves, compared to other populations.[14] It is important to ensure Aboriginal peoples living with opioid use disorder have access to quality, culturally-appropriate care which warrants the need to conduct high quality research in this population.

4.5 LIMITATIONS

While my systematic review was conducted meticulously to meet Cochrane review standards, it does have a number of limitations.

The included trials failed to include any Canadian research articles to adequately reflect how opioid use disorder could be managed in a Canadian primary care setting. While extrapolating the results from U.S. and European studies is commonly done in research, the uniqueness of primary care settings globally makes it challenging to do so in this review.

All research was conducted prior to changes made to the DSM criteria for diagnosis of opioid use disorder. This new set of diagnostic criteria may offer insight into a population not fully represented in our current body of literature. Further, only two studies utilized DSM criteria for their enrollment of participants, while other studies chose to include patients already stabilized in methadone maintenance programs or who had opioid-positive urines. This could suggest that some patients with opioid use disorder were overlooked, including patients with chronic pain who were prescribed opioids.

While the majority of included trials were conducted over 26-52 weeks, the timeframe was not adequate to capture long-term, meaningful outcomes in this population. Though treatment retention and opioid abstinence function as surrogate endpoints in this condition, they should not replace further research on infectious disease transmission, fatal and non-fatal overdose, hospitalizations, emergency department visits and mortality.

While the search strategy for this review was comprehensive and included a grey literature search, there is the potential that new or unpublished literature was not captured.

Finally, while the dissemination of the Tools for Practice related to the systematic review findings was sent to a large, nationally representative sample of family physicians, it would have

been interesting to conduct a survey to determine how many physicians implemented the findings into their practice.

4.6 CONCLUSIONS

While the body of evidence reviewing treatment settings for patients with opioid use disorder has its limitations, findings suggest that primary care offers an equivalent to superior option to specialty care settings in the management of opioid use disorder.

Results found higher proportions of opioid-abstinence and satisfaction in patients treated in primary care settings. Where reported, adverse events were similar between settings.

It is important to recognize the resources and training that were available to primary care providers. Often, primary care providers had previous experience or training in management of opioid use disorder, proposing that those providers may be the first to adopt these new findings and implement opioid agonist therapy in their practices. It is important for healthcare systems to ensure that access to support and training are available to support the transition for primary care providers, offering management of opioid use disorder for the first time.

It is also important for future research to focus on the Canadian primary care setting, including higher risk populations, Aboriginal peoples, those with co-morbid substance use or psychiatric conditions and those who are unemployed or facing homelessness.

Primary care is uniquely placed to provide care for patients with opioid use disorder, decreasing the wait-time for opioid agonist therapy, cultivating continuity of care and improving health outcomes for this high-risk patient population.

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