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Laxatives and Erectile Dysfunction Medications to Treat Side Effects of Opioid Agonist and Methadone Maintenance Therapy

Rapid Review

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Abbreviations

ED	erectile dysfunction
MMT	methadone maintenance therapy
OAT	opioid agonist therapy
OUD	opioid use disorder
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Key Messages

- Opioid agonist and methadone maintenance therapies are essential medical interventions for effectively managing opioid use disorder. However, side effects, including constipation and erectile dysfunction can compromise treatment adherence and increase the risk of relapse.
- No studies or guidelines describing the clinical effectiveness or recommendations for the use of laxatives or erectile dysfunction medications in the treatment of constipation or erectile dysfunction in patients undergoing OAT or MMT were identified.
- Research is needed to understand the clinical effectiveness and inform guidance concerning the treatment of constipation with laxatives and the use of medications indicated for erectile dysfunction.

Context and Policy Issues

Opioid use disorder (OUD) is a health crisis in Canada[1,2] and around the world.[3,4] OUD is characterized by a dependency on opioid drugs and/or prescription opioid medications, and people living with OUD experience a euphoria commonly known as "getting high."[5] People of all ages and/or sociodemographic backgrounds can develop OUD; however, known risk factors include younger age (i.e., adolescents and young adults), a history of substance abuse, and/or comorbid mental illness.[6] People living with OUD often experience significant morbidity and mortality, including loss of livelihood and/or social networks and supports, homelessness, increased hospitalization, and death.[2,4,7,8] Increasingly, the opioid crisis is being driven by the misuse of opioid medications that are commonly prescribed for patients experiencing pain — in particular, chronic pain.[8]

Treatment for OUD is generally multi-modal, including both behavioural and pharmacological interventions.[4,5,9] Opioid agonist therapy (OAT) and methadone maintenance therapy (MMT) are effective medical interventions for reducing the symptoms of dependency and supporting patients with OUD to reduce and abstain from their misuse of opioids.[1,10] OAT and MMT medications include methadone and buprenorphine, which are longer-acting opioid medications as compared to the shorter-acting opioid drugs and medications that can cause OUD.[4] OAT and MMT thereby reduce the symptoms of withdrawal without producing the effect of getting high.[9] However, like all opioid medications and drugs, OAT and MMT cause side effects, such as constipation and sexual dysfunction (including erectile dysfunction [ED] in men).[11] These side effects can cause discomfort and distress, and may discourage patients undergoing OAT or MMT from continuing with treatment, which can increase the risk of relapse.[12,13]

Constipation has been described as a common and persistent side effect of OAT and MMT.[9-11] Opioid-induced constipation is a side effect common to all opioid drugs and medications, and is described as one of the most common gastrointestinal adverse effects caused by this class of drugs.[14] In addition to more serious complications from chronic constipation, it can cause bloating, discomfort, and reduced quality of life for affected patients.[15] Common treatments for constipation include dietary and lifestyle interventions (such as increased fibre and/or exercise) and/or laxatives (including stimulants, stool softeners, and fibre supplements).[16] Although there is some information and evidence to inform the treatment of opioid-induced constipation in patients receiving prescribed opioids,[17-19] less information is

known to be available to inform best practices for treating OUD patients with constipation as a side effect of OAT or MMT.

Sexual dysfunction is also a side effect of opioid drugs and medications — including OAT and MMT — and can occur in both men and women.[20-23] Sexual dysfunction causes a variety of deleterious symptoms, including abnormalities in sexual desire, arousal, and satisfaction,[13] and sometimes resulting in ED for men.[24] Sexual dysfunction and/or ED may have various underlying causes, including those of a physiologic, social, and/or psychological etiology.[12,25] The association between exposure to OAT and sexual dysfunction (including ED) is well-established.[12,25] Treatments for ED in the general population may include medical, mechanical, and/or surgical interventions[26]; however, less information is known to be available to inform best practices for the treatment of ED as a side effect of OAT or MMT in patients living with OUD.

Given the benefits that OAT and MMT can offer to patients living with OUD — as well as the known side effects of these medications and the limited information available to inform treatment to reduce their deleterious effects — there is a need to assemble and assess available evidence addressing this topic. Thus, the purpose of this report is to identify and summarize evidence and guidelines describing the clinical effectiveness and/or recommendations to inform the use of laxatives and/or ED medication for OUD patients undergoing OAT or MMT.

Research Questions

1. What is the clinical effectiveness of laxatives to treat constipation in patients undergoing opioid agonist therapy or methadone maintenance treatment?
2. What is the clinical effectiveness of erectile dysfunction medication to treat sexual dysfunction in patients undergoing opioid agonist therapy or methadone maintenance treatment?
3. What are the evidence-based guidelines regarding laxatives or erectile dysfunction medication for patients undergoing opioid agonist therapy or methadone maintenance treatment?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE All via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were OAD or MMT and drug therapy for constipation and ED. Search filters were applied to part of the search to limit retrieval to guidelines. When possible, retrieval was limited to the human

population. The search was also limited to English-language documents published between January 1, 2016, and May 11, 2021. Internet links were provided if available.

Selection Criteria and Methods

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

Exclusion Criteria

Articles were excluded if they did not meet the eligibility criteria outlined in Table 1, were duplicate publications, or were published before 2016. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

Critical appraisal was not undertaken because no eligible guidelines were identified.

Summary of Evidence

Quantity of Research Available

A total of 397 citations were identified in the literature search. Following screening of titles and abstracts, 359 citations were excluded and 38 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant source was retrieved from the grey literature search for full-text review. Of these potentially relevant

Table 1: Selection Criteria

Criteria	Description
Population	Patients undergoing opioid agonist therapy or methadone maintenance treatment (i.e., suboxone, morphine, or naltrexone)
Intervention	Q1: Laxatives, bulk-forming agents, and stool softeners (e.g., docusate, senna, polyethylene glycol 3350, sodium phosphate, bisacodyl, glycerine suppositories, psyllium husk) Q2: Erectile dysfunction medication (e.g., sildenafil citrate, tadalafil, vardenafil) Q3: Laxatives, bulk-forming agents, and stool softeners, or erectile dysfunction medication
Comparator	Alternative medications for constipation or sexual dysfunction; non-pharmacological; alternative lifestyle changes; no treatment
Outcomes	Q1 and Q2: Clinical effectiveness (e.g., change in symptoms, safety) Q3: Recommendations regarding the use of laxatives or erectile dysfunction medication in patients undergoing opioid agonist therapy or methadone maintenance treatment
Study designs	HTAs, systematic reviews, randomized controlled trials, non-randomized studies, evidence-based guidelines

HTA = health technology assessment.

articles, 39 publications were excluded for various reasons, and no publications met the inclusion criteria and were included in this report. Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[27] flow chart of the study selection.

Additional references of potential interest are provided in Appendix 2.

Summary of Findings

No studies assessing the clinical effectiveness of laxatives to treat constipation or ED medications to treat sexual dysfunction medications for patients undergoing OAT or MMT were identified. No evidence-based guidelines informing the use of laxatives or ED medications for patients undergoing OAT or MMT were identified; therefore, no summary is provided.

Limitations

No eligible studies nor evidence-based guidelines describing laxatives or ED medications for patients undergoing OAT and MMT were identified.

Conclusions and Implications for Decision- or Policy-Making

No evidence or evidence-based guidelines describing the use of laxatives or ED medication to treat the side effects of OAT or MMT were identified. This gap in the evidence describing treatment of the side effects of OAT and MMT has also been acknowledged in the literature reviewed for this report.[22] Most of the evidence in this topic area was found to address either the clinical effectiveness of OAT and/or MMT[28,29] or the side effects from prescribed opioid medications in patients living with pain.[17-19,30,31] Although existing guidelines offer recommendations about the use of OAT and/or MMT to treat OUD, there were no guidelines identified informing the management or treatment of constipation or ED as side effects of OAT and/or MMT.[1,8]

CADTH has previously assembled a body of evidence relevant to opioids,[32,33] including reports that have assessed and summarized evidence specific to the use of OAT and MMT and its effects on people living with OUD.[34-38] One recent CADTH report assembled and summarized qualitative evidence describing the experiences of OUD patients and described a preference among some patients for buprenorphine as compared to methadone due to the perception of fewer side effects with the former.[39] However, the CADTH reports produced to date have not addressed treatment of side effects from OAT.

Several sources were identified in this review that described investigations into the treatment of constipation as a side effect of opioid medication prescribed for patients with chronic pain[17-19,30]; however, there were no studies that described the treatment of constipation as a side effect of OAT or MMT. Notably, the sources identified did not describe investigation into the use of laxatives to treat opioid-induced constipation; rather, these studies assessed the use of naldemedine[17,30] and methylnaltrexone.[18,19]

Several studies that assessed sexual dysfunction and/or ED were identified but did not meet the eligibility criteria for this review — many were observational and, as such, did not assess an intervention.[12,24,25,40] Two such studies assessed measures of sexual dysfunction and/or ED and other psychological parameters in men living with OUD and receiving MMT as

compared to men not receiving MMT. Authors of both studies reported finding significantly more sexual dysfunction and/or ED and psychological morbidity among patients receiving MMT.[12,25] Another study reported a significant correlation between psychological distress and ED in patients receiving MMT.[24] Authors of these and other studies addressing sexual dysfunction and/or ED have highlighted the importance of multiple variables that often contribute to the problem of sexual dysfunction and ED — in this case, among patients receiving OAT and MMT.[12,24,25,40] The complexity of ED is likely to contribute to the challenge of effective treatment, and may be compounded in patients receiving OAT and/or MMT given the psychological, sociological, and other comorbidities that can occur in these patients.

Several other studies were identified that investigated the use of alternative therapies[20,22,23,41,42] and/or antidepressant drugs[41-43] as primary study interventions for the treatment of ED as a side effect of MMT as opposed to investigating ED medication. One such study reported an improvement in ED for MMT patients receiving Rosa damascena oil as compared to those randomized to placebo.[22] Another double-blind, placebo-controlled randomized trial reported that ginseng produced a benefit to both male and female patients with sexual dysfunction as a side effect of MMT.[20] Yet another study randomized MMT patients to either crocin or placebo and measured psychological parameters after 8 weeks (including ED); the authors reported a statistically significant improvement in patients receiving the active intervention.[42] Nonetheless, the treatment of ED using medications developed for the condition itself (e.g., sildenafil citrate, tadalafil, vardenafil) was not described in the studies identified by this review.

Given the importance of OAT and MMT in the context of the opioid crisis, and the risk that side effects such as constipation and/or ED may pose to treatment adherence, there is a need for more research investigating best practices and interventions to inform the management of care and ensure optimal patient outcomes.

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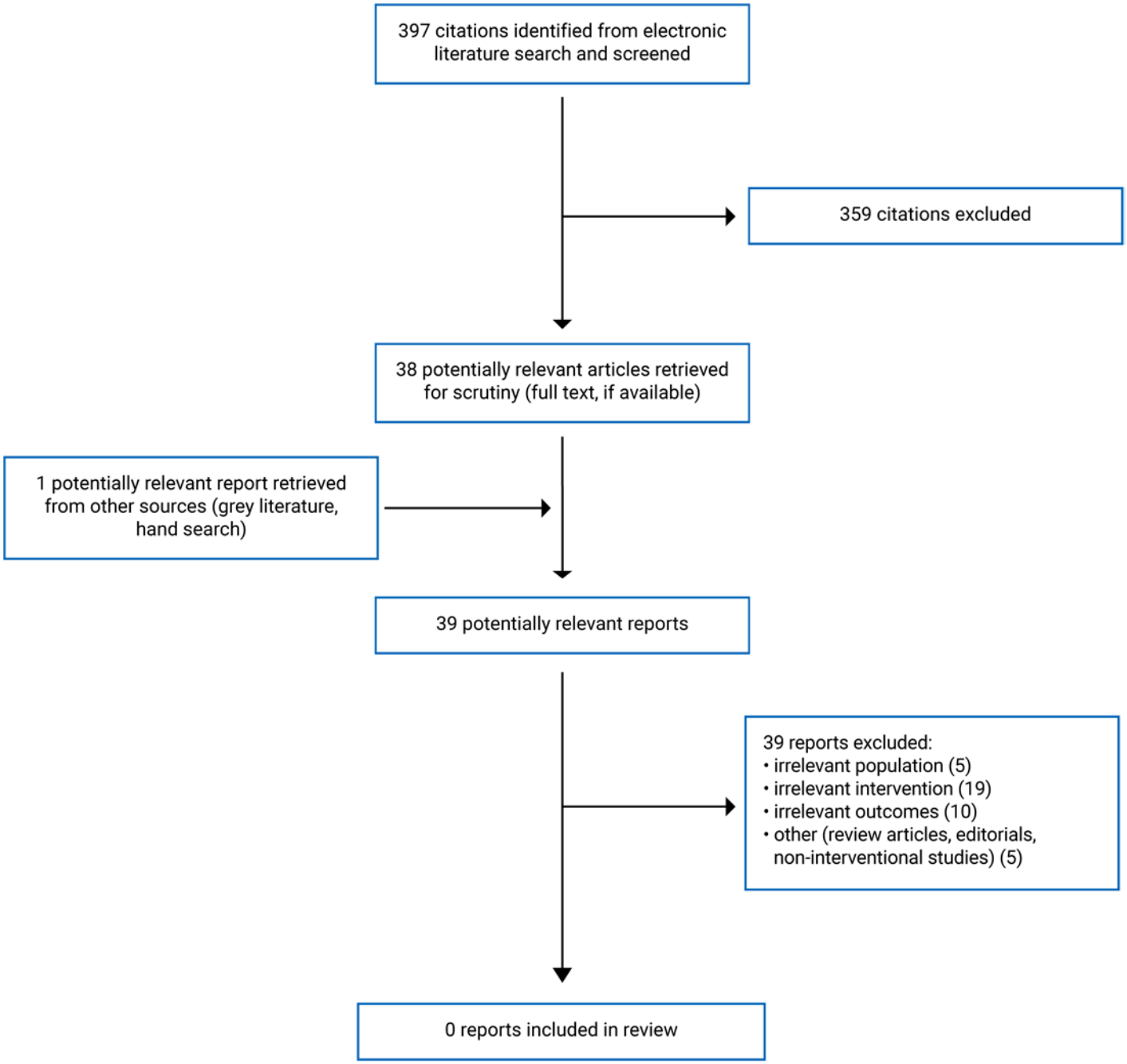
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



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