Lacking evidence for the association between frequent urine drug screening and health outcomes of persons on opioid agonist therapy

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ABSTRACT

Background: Opioid agonist therapy (OAT) is a first-line treatment for opioid use disorder (OUD); however, the efficacy and role of urine drug screening (UDS) in OAT has received little research attention. Prior evidence suggests that UDS frequency reflects philosophy and practice context rather than differences in patient characteristics or clinical need. Therefore, we reviewed the literature on the effect of and recommendations for the frequency of UDS on health outcomes for persons with OUD who receive OAT.

Methods: We searched Medline and EMBASE for articles published from 1995-2017. Search results underwent double, independent review with discrepancies resolved through discussion with a third reviewer, when necessary. Additional articles were identified through snowball searching, hand searching (Google Scholar), and expert consultation. The Cochrane tool was used to assess risk of bias.

Results: Of the 60 potentially eligible articles reviewed, only one three-arm randomized open-label trial, comparing weekly and monthly UDS testing with take-home OAT doses, met our inclusion criteria.

Conclusions: Our review identified an urgent gap in research evidence underpinning an area of clinical importance and that is routinely reported by patients as an area of concern.

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Keywords: *urine drug screening, urinalysis, office-based opioid treatment, opioid agonist treatment, hospitalization, substance-related disorders*

INTRODUCTION

Opioid use disorder (OUD) is a chronic condition impacting the reward, motivation and memory pathways of the brain (ASAM, 2017). Mortality associated with OUD is a growing concern, with more than half of global deaths caused by illicit drug use attributed to OUD in 2010 (Degenhardt et al., 2013). In 2015, there were approximately 33,000 deaths due to opioid overdose (illicit and prescription) in the United States - the leading cause of accidental death that year (Rudd, 2016).

OUD is a treatable condition with effective pharmacological and behavioural interventions (Amato, Minozzi, Davoli, & Vecchi, 2011). The recommended first-line treatment for OUD stabilization is opioid agonist therapy (OAT), the use of either a full opioid agonist (methadone) or a partial opioid agonist (buprenorphine/naloxone) in addition to psychosocial treatment (Degenhardt et al., 2013). Despite its benefits, relatively low proportions of primary care practitioners prescribe OAT effectively, and few learners are given formal training on the continuum of care for OUD patients (Klimas, Tobin, Egan, Tomas, & Bury, 2016).

In the context of OUD care, Urine Drug Screening (UDS) is used as either i) a screening tool (i.e., presumptive), conducted in the point of care setting, or ii) a confirmatory test (i.e., definitive), generally conducted in the laboratory setting (ASAM, 2017). In primary care, UDS can be used to detect or validate self-reported drug use in OUD treatment (Barthwell, 2016; British Columbia Centre on Substance Use & CIHR Canadian Research Initiative on Substance Misuse, 2017), and monitor adherence to OAT. In this context, the frequency of UDS could have significant impacts on retention and adherence to treatment, with higher frequency schedules potentially resulting in greater benefits to OAT-treated patients. However, costs can sometimes be a barrier to the regular use of UDS in clinical settings,

which are dependent on the type of tool and laboratory technique used. Generally, screening is less expensive than confirmatory testing (Barthwell, 2016). Appropriate scheduling of UDS is therefore essential for providing optimal OUD care, while minimizing health system costs resulting from unnecessary and expensive testing. When determining UDS schedules in OAT-treatment settings, many turn to provincial or federal guidelines (reviewed in a previous report by Moss et al., 2018), which often lack consistency and rely primarily on expert opinion.

Although urine screening is the focus of this report, it is important to note alternative biological samples that can be used in drug testing, including hair and oral fluid. Though not as commonly used, these samples may be less prone to falsification and therefore represent potential improvements to urine testing in the context of OAT.

A recent review by Dupuoy et al. (2014) has summarized the evidence pertaining to the efficacy of UDS for medical management, but did not specifically examine the frequency of this testing. Gaps in our understanding of the role of UDS persist, despite its importance for clinicians and patients. Pragmatic intervention studies exploring a range of testing schedules in daily settings in order to obtain an accurate picture of UDS protocol usefulness are lacking (Dupouy et al., 2014). The need for this type of analysis is further highlighted by the most recent draft of "The American Society of Addiction Medicine's Drug Testing Appropriateness Document" (ASAM, 2017), which was recently approved by the Board of Directors (April 5, 2017). In the current review, we therefore sought to assess the clinical evidence for the effectiveness of different frequencies of UDS for persons with OUD who are receiving OAT.

METHODS

Included studies must have met the following criteria: (1) focused on a population of individuals with substance use disorders (SUD) accessing OAT; (2) used UDS as an intervention; (3) compared different frequencies of UDS; (4) evaluated health-related outcomes, including quality adjusted life years, blood borne pathogen infection, and overdose; and (5) took place in an inpatient or outpatient setting. Particular UDS characteristics that may result in bias, such as the presence of observed screening, were planned to be dealt with on a case-by-case basis. We excluded case studies, non-English language studies, animal studies, studies not presenting original data (e.g., conference proceedings, abstracts), and studies of patients being treated for chronic pain. In order to meet quality cut-offs, included studies had to demonstrate at least three of the following features: randomization, allocation concealment, blinding of participants and staff, blinding of UDS outcomes, little-to-no attrition bias, and/or little-to-no reporting bias, as outlined by the Cochrane risk of bias tool (Higgins & Green, 2011). To identify relevant high-quality articles, we searched Medline from 1995 to March 2017, and Embase from 1995 to September 2017. The search strategy incorporated terms such as *"urine drug test", "drug abuse screening",* and *"urinalysis"* (July 2016 and September 2017), as well as subject heading terms *"substance abuse detection"* (March and April 2017) and *"drug screening"* (September 2017, see Appendix for full search strategy). Articles were also identified through a snowball search, hand searching (Google Scholar), and expert consultation. In addition, the reference lists of Dupouy et al's (2014) review on UDS were reviewed. Articles were screened according to PRISMA guidelines (Liberati et al., 2009), and two reviewers independently reviewed full texts of potentially relevant articles. Data extraction was conducted independently by JK and JM. Disagreements were resolved by consensus, or by an independent third reviewer, if necessary. Included articles were assessed using the Cochrane

risk of bias tool, which rates studies as high, low, or uncertain risk of bias for six domains (Higgins & Green, 2011).

RESULTS

We identified 3795 potentially eligible unique citations from the Medline and EMBASE databases, Google searches, hand searching, bibliography searching and expert contact. Titles and abstracts were screened using the pre-specified inclusion criteria (Figure 1), with the main reason for exclusion being a lack of information on UDS frequency as our primary outcome of interest (n=3543). Though not examining UDS frequency, many of these studies involved UDS and were therefore captured in our search. Overall, 60 studies were found to be eligible for full-text review, of which 59 were excluded due to UDS frequency not being an independent variable (n=43), those on OAT not being the study population (n=12), being a conference abstract (n=1), or not including original data (n=3). Of the eight studies included in a previous, similar review by Dupouy et al. (2014), none were found to be eligible for inclusion in the current study. Reasons for exclusion included the study population not being patients with SUD and/or OAT (n=7) and being outside of the included publication dates (n=1). Only one full text report met our eligibility criteria (Chutuape, Silverman, & Stitzer, 2001).

This three-arm randomized open-label trial (N = 53) compared treatment outcomes for participants receiving take-home doses of methadone. All participants in the included study were patients enrolled in a methadone outpatient clinic – 60% were male; mean age of 38 years. The duration of the trial was 28 weeks. Participants assigned to the intervention groups received take-home doses contingent on random weekly or monthly negative UDS tests for opiates or cocaine. The control group received take-home doses randomly,

independently of the testing result. Based on a "time-course analysis" this study found that take-home doses, contingent on drug-free urines, prevent a decline in treatment performance and retention over time, sustained with testing as infrequently as once per month. After assessing Chutuape et al. with the Cochrane risk of bias assessment tool (Higgins & Green, 2011), the study was determined to be of a high risk of bias due to a lack blinding of treatments, an unclear allocation concealment and blinding of outcomes (see details of quality rating and study characteristics in Table 1).

DISCUSSION

Our critical review of literature suggests that there is very little evidence on the effectiveness of UDS on patient or community health outcomes. It identified an urgent gap in research evidence underpinning an area of clinical importance and that is routinely reported by patients as an area of concern. These results concur with findings of a previous review of the literature up to 2011 by Dupouy et al. (2014), demonstrating insufficient evidence for using UDS in medical management. Similar to their findings, we found just one clinical trial evaluating the effect of UDS frequency on health outcomes.

This limited literature-base is likely influenced by a number of factors. These include differences between opioid agonists, insufficient attention paid to UDS in the context of OAT versus chronic pain, random versus fixed schedules, and the clinical judgment and autonomy of physicians. First, buprenorphine/naloxone, now considered to be first-line treatment for OUD (British Columbia Centre on Substance Use & CIHR Canadian Research Initiative on Substance Misuse, 2017), has a more favourable safety profile then methadone, and the UDS frequency recommendations are less clear and more under the discretion of clinicians. Second, UDS in the context of OAT has historically received less research attention compared to UDS in chronic pain patients prescribed opioids (Starrels et al., 2010). Most

trials involving chronic pain patients often specifically exclude people with substance use disorders (Busse et al., 2017). Nevertheless, the On-Site Evaluation of Substances Consumption on Opiate Maintenance (ESUB-MG) cluster-randomized trial is underway (Esub-Mg Study Group, 2016), which will compare OAT retention of patients starting on buprenorphine/naloxone receiving UDS at the discretion of a physician, with a similar control group not receiving UDS testing. Third, random UDS is more likely to detect other substances, such as amphetamines or benzodiazepines, than a fixed schedule UDS, since many substances have a relatively short half-life in the body; however, this poses a challenge in rural settings where resources for UDS are limited. It may therefore be difficult to accurately capture different UDS frequencies in this context. Fourth, over-reliance on clinical judgement, even in guidelines, is a major feature of the literature, although it is prone to errors in cognitive reasoning. Future research should therefore strive to take these reasons for high variability into account.

Our critical review of the evidence is limited in several ways. Only three electronic biomedical databases were searched (two biomedical plus Google Scholar). It is possible that we missed studies, and, as such, our search cannot be taken as a thorough representation of the UDS literature. The exclusion of chronic non-cancer pain studies reduces the scope of our work, yet many important studies on opioids for non-cancer pain have been published (Starrels et al., 2010). The small numbers of studies included could also be explained by the time period searched (limited to 1995-2017), and the removal of studies that were not in the English language.

Overall, this critical review suggests that there is insufficient evidence on the effectiveness and impact of UDS testing frequency for persons on OAT. Additional research

is required to articulate the relationship between urine drug screening frequency and health outcomes in this context.

Authors' contributions
JM, LAW, EM, LG and KP participated in the design of the study, performed the literature review, classified the findings and drafted the manuscript. JK participated in the design of the study and contributed to the manuscript. EW contributed to the manuscript. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

Ethical approval
Research described in this manuscript adheres to international ethical standards; we conducted a critical review of literature for which no approval from a named research ethics committee was required.

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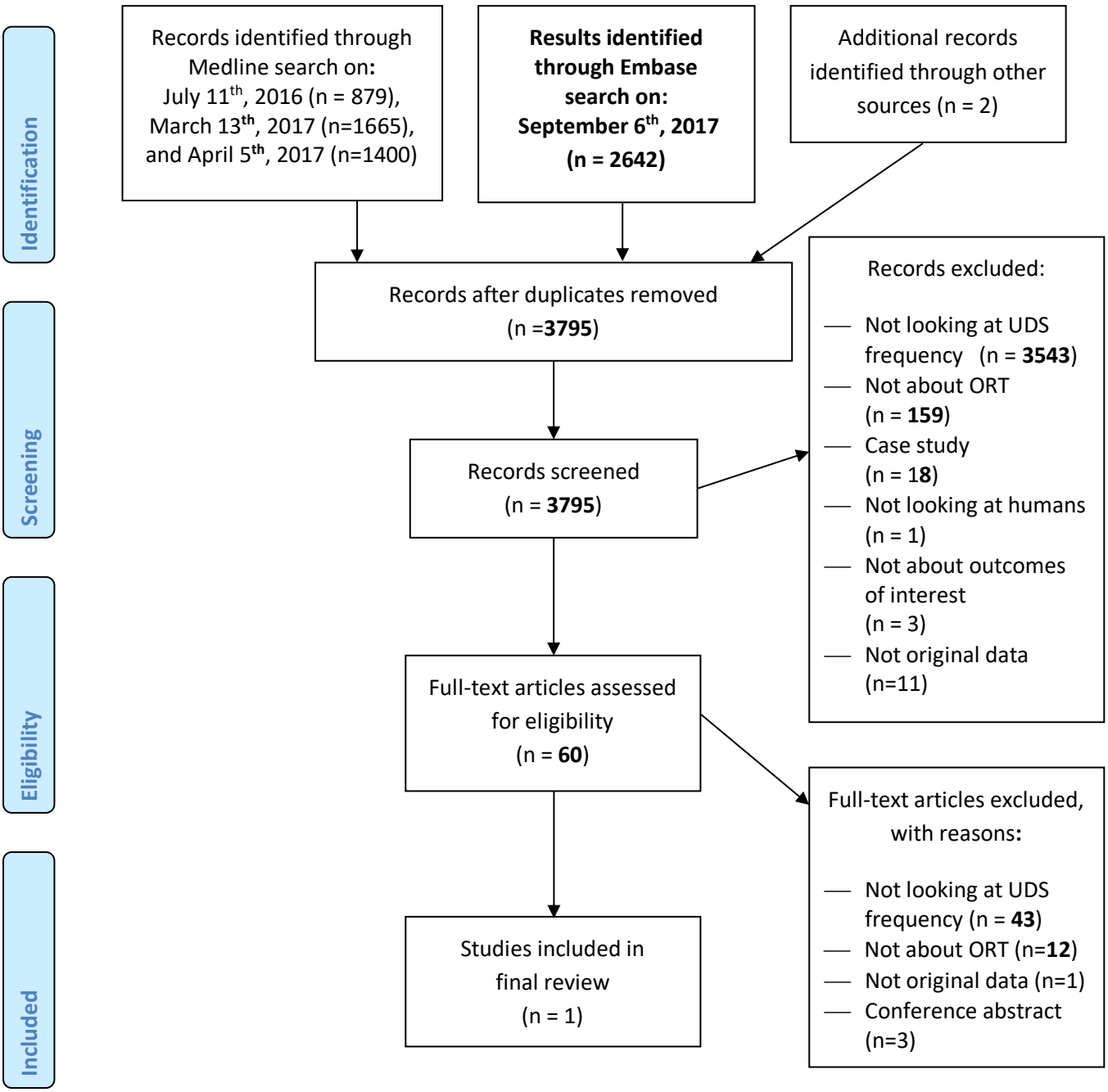
Table 1 Study characteristics

Author, Year	Design	Study population	Location	Intervention/ Control	Results	Risk Rating* A B C D E F
Chutuape et al., 2001	Randomized control trial (unblinded)	53 outpatient methadone clinic patients who have completed 5 weeks of baseline treatment	Baltimore, USA	Weekly or monthly testing with contingency management (intervention); monthly testing with random contingency management (control)	***Retention*** (weekly had significantly more drop-out than the random drawings group; total of 10 drop outs, n=6 from weekly, n=3 from monthly, n=1 from random); ***Time course analysis of opiate/cocaine urine sample results*** (for % drug-negative samples there was a significant main effect of group [p<0.04] but no significant difference for the time or group x time interaction p>0.10; for percent opiate negative samples over time there was a significant main effect of group [p<0.04] but no significant time effects, group x time interaction, or post-hoc pairwise comparisons); ***Consecutive weeks of abstinence*** (mean longest duration of opiate and cocaine-free urines was 10.5 week, 8.4 month, 5.4 random [p<0.16]); ***Percent with at least 8 weeks of abstinence*** (weekly 56.6, 38.9 monthly, random 10.5, p<0.002, weekly had significantly more meeting the 8 week abstinence than random group p<0.02)	+ - + +

Appendices: Online supplementary material

Appendix 1. Study flow diagram



Appendix 2: PubMed/MEDLINE and EMBASE Search Strategy

1995-July 11th, 2016	1995-March 13th, 2017	1995-April 5th, 2017	1995-September 6th, 2017 – EMBASE
1. Urin*.ti,ab. 2. Urinalysis/ 3. 1 or 2 4. Emergency room.ti,ab. 5. Emergency department.ti,ab. 6. Hospitali#*.ti,ab. 7. Mortalit*.ti,ab. 8. Overdose.ti,ab. 9. Blood borne virus.ti,ab. 10. Blood borne pathogen.ti,ab. 11. Hepatitis c.ti,ab. 12. Human immunodeficiency virus.ti,ab. 13. HCV.ti,ab. 14. HIV.ti,ab. 15. Blood-Borne Pathogens/ 16. Drug Overdose/ 17. exp Mortality/ 18. Emergency Service, Hospital/ 19. exp HIV Infections/ 20. exp Hepatitis C/ 21. exp hospitalization/ 22. exp Substance-Related Disorders/ 23. Street Drugs/ur 24. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 25. Methadone.ti,ab. 26. suboxone.ti,ab. 27. (Buprenorphine and naloxone).ti,ab. 28. exp Methadone/ 29. exp Buprenorphine/ 30. exp Buprenorphine,	1. Urin*.ti,ab. 2. Drug Abuse Detection.ti,ab. 3. Drug Abuse Screening.ti,ab. 4. Drug Abuse Testing.ti,ab. 5. Illicit Drug Detection.ti,ab. 6. Illicit Drug Testing.ti,ab. 7. Drug Screening.ti,ab. 8. Urinalysis/ 9. Urine Specimen Collection/ 10. Substance Abuse Detection/ 11. Drug Evaluation, Preclinical/ 12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 13. Emergency room.ti,ab. 14. Emergency department.ti,ab. 15. Hospitali#*.ti,ab 16. Mortalit*.ti,ab. 17. Overdose.ti,ab. 18. Blood borne virus.ti,ab. 19. Blood borne pathogen.ti,ab. 20. Hepatitis c.ti,ab. 21. Human immunodeficiency virus.ti,ab. 22. HCV.ti,ab. 23. HIV.ti,ab. 24. Blood-Borne Pathogens/ 25. Drug Overdose/ 26. exp Mortality/ 27. Emergency Service, Hospital/	1. Urine Drug Abuse Screen*.mp. 2. Illicit Drug Detection.mp. 3. Illicit Drug Test*.mp. 4. Urine Drug Screen*.mp. 5. exp Urinalysis/ or exp Urine Specimen Collection/ 6. urine drug test*.mp. 7. urine drug*.mp. 8. exp Substance Abuse Detection/ 9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 10. Morphine Dependence.ti,ab. 11. exp Narcotics/ or exp Opioid-Related Disorders/ or exp Opiate Substitution Treatment/ or exp Buprenorphine/ or exp Methadone/ or exp Heroin Dependence/ or exp Prescription Drug Misuse/ or exp Buprenorphine, Naloxone Drug Combination/ or exp Opium/ 12. 10 or 11 13. 9 and 12 14. Animals/ 15. Humans/ 16. 14 not (14 and 15) 17. 13 not 16 18. limit 17 to (english language and yr="1995 -Current")	1. Illicit Drug Detection.ti,ab. 2. Illicit Drug Test*.ti,ab. 3. Urine Drug Screen*.ti,ab. 4. Urine drug test*.ti,ab. 5. Urine drug*.ti,ab. 6. Urinalysis/ 7. Drug screening/ 8. Drug urine level/ 9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 10. Methadone.ti,ab. 11. Suboxone.ti,ab. 12. (Buprenorphine and naloxone).ti,ab. 13. Opiate/ 14. Opiate agonist/ 15. Narcotic dependence/ 16. 10 or 11 or 12 or 13 or 14 or 15 17. 9 and 16 18. limit 17 to (human and english language and yr="1995 - Current")

Naloxone Drug Combination/ 31. exp Opiate Substitution Treatment/ 32. 25 or 26 or 27 or 28 or 29 or 30 or 31 33. 3 and 24 and 32 34. limit 33 to (english language and humans and yr="1995 -2016")	28. exp HIV Infections/ 29. exp Hepatitis C/ 30. exp hospitalization/ 31. exp Substance-Related Disorders/ 32. Street Drugs/ur 33. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 34. Methadone.ti,ab. 35. suboxone.ti,ab. 36. (Buprenorphine and naloxone).ti,ab. 37. Morphine Dependence.ti,ab. 38. exp Methadone/ 39. exp Buprenorphine/ 40. exp Buprenorphine, Naloxone Drug Combination/ 41. exp Opiate Substitution Treatment/ 42. exp Opioid-Related Disorders/ 43. Opium/ 44. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 45. 12 and 33 and 44 46. limit 45 to (english language and humans and yr="1995 - Current")		