PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Evaluating the association between urine drug screening frequency and retention in opioid agonist treatment in Ontario, Canada: A Retrospective Cohort Study
AUTHORS	Morin, Kristen; Dabous, John; Vojtesek, Frank; Marsh, David

VERSION 1 – REVIEW

REVIEWER	Batki, Steven
REVIEW RETURNED	29-Mar-2022

GENERAL COMMENTS	This paper addresses an important and under-studied question. The following are a few questions/comments to the authors: p.2 Abstract: the abstract should include at least a brief reference to the limitations referenced on page 2 -- it was not clear to this reviewer whether the "strengths and limitations" were included as a part of the abstract or not. p.4, line 37-- ascribing the high risk of OD mortality to "changes in opioid tolerance" may not be entirely accurate p.5 methods: please describe how many different treatment clinics are represented by the 55,921 adults Please discuss what accounts for the variations in urine drug screening frequency? Does any given clinic apply its own policy of UDS frequency to the treatment of patients? Do clinics have different policies? Why are some patients tested more and others less frequently? The basic uncertainty this reviewer is faced with involves the fundamental question of what drives the determination of UDS frequency? Is it clinic-specific policy that is then applied to all patients? or do clinics vary the frequency of testing based on patient characteristics? Either way there is risk of confounds. The lack of patient descriptors that assess addiction severity is a major weakness that the authors acknowledge. Please indicate how the determination of "mental health conditions" as if information beyond just the dichotomous "yes" or "no" is available, presentation of that data may yield information about severity differences in the cohort.

	Is it possible that "better" or "higher quality" clinics conduct more UDS testing? Is it possible that more severely ill patients would self-select clinics with lower UDS frequency? The "monthly or less" group may be more severely ill, given the significantly higher soft tissue infection prevalence. This was discussed by the authors. p.12: the authors state the need to assess UDS frequency differences in buprenorphine vs methadone treated patients -- they do not say why they did not conduct this analysis on the study cohort. Please address the somewhat contradictory dynamics of better performance in treatment leading to less frequent urine testing over the course of treatment-- but, wouldn't it also lead to greater retention?

REVIEWER	Jamshidi, Nazila Royal Prince Alfred Hospital, Drug health services
REVIEW RETURNED	11-Apr-2022

GENERAL COMMENTS	Thank you for the request to review this paper which attempts to decipher whether frequency of UDS is associated with retention in OAT. The strengths of this study include the large cohort number, well presented and well written. However the study's findings seem superficially addressed with in the discussion. The weakness include the retrospective study observational design, the data collection as highlighted by the authors not being for research purposes and thus motivations for UDS collection somewhat punitive for clients. Although the study identified greater retention in OAT with clients having weekly UDS. There are several factors that are not clearly explained, these include: - The demographic data dividing patients into regions does not clearly define what the patient's socioeconomic status and access to clinics is in each area. Although barriers are explained for northern rural regions, they are not for other areas. The international reader cannot ascertain whether in areas that low number of uds are performed are as a result of lack of access to clinics or more stable patients in the first place. This needs to be more fleshed out in part in the results) potentially with maps and clinics) and then in the discussion. How many of these patients are under court order or required by law to give such frequent UDS? Was it part of a a legal requirement and hence the high retention (i.e. retention in some areas had nothing to do with uds rather it had to do with the cohort being under close police surveillance and hence the higher retention, this needs to be explored) - How do these guidelines compare internationally. In some jurisdictions UDS is only done at baseline and 3/12 , yet retention rates are still high, yet in others UDS are performed only if it they alter the outcome of treatment (eg if patient is intoxication or suspected to divert). - Although the authors highlight unmeasured confounders associated with retention no effort has been made to explore these - Finally what about the rate of false positive and false negative UDs, did this have a role in the rate of retention.

	Given the retrospective and longitudinal data collected the authors could have easily looked at 1, 3 and 5 year retention rates of clients and commented on this. I feel that this would greater value to the study and determine whether current Canadian guidelines are useful or not. In general UDS should not guide treatment but act as adjunct to current care to assist with enhancement of services if required in those still using or involved in polysubstance use. Frequent UDS are a waste of laboratory resources and do not improvement of care to patients. An important limitation is not identifying or performing" matched" groups in each region to control for confounders. The authors may wish to do this to rule out area bias for their findings. Recommendation: - For publication if the authors are able to address the concerns addressed above

REVIEWER	Sobel, Halle University of Vermont Health Network, GIM
REVIEW RETURNED	11-Apr-2022

GENERAL COMMENTS	This is a very important topic and discussions on the frequency of UDS need to be added to the literature. I am not sure if we can conclude that there is a direct link (cause and effect) between frequency and retention. I wonder what the reasons were for lack of retention? What happened to these patients if they had an abnormal UDS? I think stable primary care patients on MOUD may be able to have less frequent testing than those in OTPs.

VERSION 1 – AUTHOR RESPONSE

Reviewer Comments	Author Response	Reference in Track changes version
Reviewer 1		
p.2 Abstract: the abstract should include at least a brief reference to the limitations referenced on page 2 -- it was not clear to this reviewer whether the "strengths and limitations" were included as a part of the abstract or not.	Thank you this has been added	Abstract, page 2
p.4, line 37-- ascribing the high risk of OD mortality to "changes in opioid tolerance" may not be entirely accurate	We softened the language and added references to support	Introduction, page 5
p.5 methods: please describe how many different treatment clinics are represented by the 55,921 adults	We added additional information, however, these data encompass all publically funded OAT in Ontario from approximately 5,000 OAT prescribers. There is no publicly	Methods - Study design and setting, page 6

	available information on the number of OAT clinics in Ontario	
Please discuss what accounts for the variations in urine drug screening frequency?	UDS frequency can vary based on patient drug use, treatment compliance, time in treatment, some physician discretion	Discussion page 12
Does any given clinic apply its own policy of UDS frequency to the treatment of patients? Do clinics have different policies? Why are some patients tested more and others less frequently?	There is a chain of clinics in Ontario that operate about 50% of OAT. This chain of clinics all follow the same provincial and clinical guidelines. However there has been some variability in physician practice in terms of frequency of urine screening and application of contingency management practices with respect to linking carry doses to drug-free urines. The study is meant to look at whether this variability impacts patient outcomes and in particular whether more frequent testing represents a barrier to retention, as some of the literature contends.	Introduction page 6
The basic uncertainty this reviewer is faced with involves the fundamental question of what drives the determination of UDS frequency? Is it clinic-specific policy that is then applied to all patients? or do clinics vary the frequency of testing based on patient characteristics? Either way there is risk of confounds.	The study is meant to look at whether this variability impacts patient outcomes and in particular whether more frequent testing represents a barrier to retention, as some of the literature contends.	Introduction page 6
The lack of patient descriptors that assess addiction severity is a major weakness that the authors acknowledge.	Thank you for your comment, this was added to the discussion	Discussion, page 13
Please indicate how the determination of "mental health conditions" as if information beyond just the dichotomous "yes" or "no" is available, presentation of that data may yield information about severity differences in the cohort.	We defined patients with mental disorders group using OHIP database diagnostic codes. The following codes are outlined in Appendix A.	Methods – study variables, p.8 and Appendix A/
Is it possible that "better" or "higher quality" clinics conduct	This is not the case here in Ontario. See comment above. Also, this is not the goal of the	

more UDS testing?	study.	
Is it possible that more severely ill patients would self-select clinics with lower UDS frequency?	It is possible, but we do not have that granularity of data to make the association	
The "monthly or less" group may be more severely ill, given the significantly higher soft tissue infection prevalence. This was discussed by the authors.	Unfortunately, we cannot respond without a specific question.	
p.12: the authors state the need to assess UDS frequency differences in buprenorphine vs methadone treated patients -- they do not say why they did not conduct this analysis on the study cohort.	Buprenorphine prescriptions frequency was very low during our study period.	Discussions, page 13
Please address the somewhat contradictory dynamics of better performance in treatment leading to less frequent urine testing over the course of treatment-- but, wouldn't it also lead to greater retention?	UDS is part of a contingency management strategy that includes increasing the number of methadone or buprenorphine/naloxone doses that a patient can take home. These take-home privileges are increased based on appointment attendance and consistently negative urine screens for opioids, cocaine, stimulants, and other substances. In Ontario, patients enrolled in OAT at specialized addiction clinics will achieve six take-home doses after at least eight months of negative UDS, which is equivalent to visiting the clinic once per week for a UDS and assessment	Introduction, page 5 and 6
Reviewer: 2		
The demographic data dividing patients into regions does not clearly define what the patient's socioeconomic status and access to clinics is in each area.	Specific clinical data is not available for this study. Rather, this is a population based study that encompasses all OAT in Ontario in all clinics.	
Although barriers are explained for northern rural regions, they are not for other areas. The international reader cannot ascertain whether in areas that low number of uds are performed are as a result of lack	Compared to many other jurisdictions, OAT is widely and readily accessible across Ontario. In most cities and towns, patients seeking OAT will receive medication on the same day. This data set does not	

of access to clinics or more stable patients in the first place. This needs to be more fleshed out in part in the results) potentially with maps and clinics) and then in the discussion.	allow the identification of the number or location of clinics.	
How many of these patients are under court order or required by law to give such frequent UDS? Was it part of a a legal requirement and hence the high retention (i.e. retention in some areas had nothing to do with uds rather it had to do with the cohort being under close police surveillance and hence the higher retention, this needs to be explored)	Although we do not have linked databases to correctional services and court orders, this is very uncommon in Ontario and Canada.	
How do these guidelines compare internationally. In some jurisdictions UDS is only done at baseline and 3/12 , yet retention rates are still high, yet in others UDS are performed only if it they alter the outcome of treatment (eg if patient is intoxication or suspected to divert).	There is very little evidence regarding the effectiveness of UDS on patient or community health outcomes in Canada and other jurisdictions. We were not able to find viable references to studies linking UDS frequency to retention rates in Canada or other jurisdictions.	Introduction page 6
Although the authors highlight unmeasured confounders associated with retention no effort has been made to explore these	We cannot respond to this comment unless the reviewer clarifies what needs to be changed.	
Finally what about the rate of false positive and false negative UDs, did this have a role in the rate of retention.	We do not have data on the rate of false positive tests. There is no evidence to our knowledge that false positive tests influence the rate of retention. The point of care immunoassay tests can be confirmed at any time through more sensitive and specific spectroscopy testing should the physician require this confirmation in order to make clinical decisions.	
Given the retrospective and longitudinal data collected the authors could have easily looked at 1, 3 and 5 year retention rates of clients and commented on this. I feel that this would greater value to the study and determine whether current Canadian	We were not able to complete this analysis for this study. However, we did just publish a paper looking at different retention times please see reference: (1)	

guidelines are useful or not.		
In general UDS should not guide treatment but act as adjunct to current care to assist with enhancement of services if required in those still using or involved in polysubstance use. Frequent UDS are a waste of laboratory resources and do not improvement of care to patients. An important limitation is not identifying or performing" matched" groups in each region to control for confounders. The authors may wish to do this to rule out area bias for their findings.	This is a popular opinion, however, as mentioned in the study, there is very limited evidence to guide clinicians. Matched groups were not possible in this study due to lower numbers in some exposure groups and low numbers in some regions.. That said, even with matching, unmeasured confounding is possible.	
Reviewer 3		
I am not sure if we can conclude that there is a direct link (cause and effect) between frequency and retention. I wonder what the reasons were for lack of retention?	We are not suggesting cause and effect, as noted in the results and discussion, we are finding associations between more frequent UDS and better treatment retention.	
What happened to these patients if they had an abnormal UDS?	We cannot respond without more clarification from the reviewer about what they mean by abnormal UDS. If they are asking whether patients with drug-positive urine tests face a OAT dose reduction or discharge from care, this is not supported by the standard of care within Ontario since 1996.	
I think stable primary care patients on MOUD may be able to have less frequent testing than those in OTPs.	We cannot respond to this comment unless the reviewer clarifies what needs to be changed. Also this data set does not allow the distinction between patients treated in a specialty addiction clinic versus those treated within a more comprehensive primary care clinic. But in Ontario the	

	regulations for these care settings are similar, thus the US distinction between OTP and OBOT is less relevant in Canada.	

1. Tahsin F, Morin KA, Vojtesek F, Marsh DC. Measuring treatment attrition at various stages of engagement in Opioid Agonist Treatment in Ontario Canada using a cascade of care framework. BMC Health Serv Res. 2022;22(1):490.

VERSION 2 – REVIEW

REVIEWER	Batki, Steven
REVIEW RETURNED	01-Aug-2022

GENERAL COMMENTS	The authors have responded adequately to the comments of the review.

REVIEWER	Jamshidi, Nazila Royal Prince Alfred Hospital, Drug health services
REVIEW RETURNED	01-Aug-2022

GENERAL COMMENTS	Thank you for the opportunity to review this report evaluating the benefits of urine drug screening and retention in opioid agonist treatment program. The strength of the study is the linkage data and the number of clients enrolled in the study. My main concern still remains with the findings of the study. The authors claim that retention is associated with increased UDS frequency. However it is more likely that the study is heavily bias in that those who where able to attend weekly appointments where always going to be engaged in treatment and had " good compliance" from the outset. The study does not explore in any depth whether these clients also had polysubstance use which improved with retention or not. Perhaps to strengthen their findings they can look at the rate of polysubstance use across the cohorts to see if frequency of UDS improves engagement. In clinical practice weekly UDS does not allow for patient autonomy and engagement back into society. The association is too weak and fraught with bias and publication can negatively impact practices in an already marginalized patient population

VERSION 2 – AUTHOR RESPONSE

Reviewer 1:

Comment 1:

My main concern still remains with the findings of the study. The authors claim that retention is associated with increased UDS frequency. However, it is more likely that the study is heavily biased in that those who were able to attend weekly appointments were always going to be engaged in treatment and had "good compliance" from the outset.

Response - This study cannot determine whether the requirement for UDS is a barrier to potential patients ever engaging in care, however, the high level of treatment engagement in Ontario compared to other jurisdictions weighs against this being a substantial factor from a public health perspective.

Reference in Main Document – Track changes: Discussed throughout the paper, specifically in the strength and limitations section and in the conclusion.

Comment 2:

The study does not explore in any depth whether these clients also had polysubstance use which improved with retention or not. Perhaps to strengthen their findings they can look at the rate of polysubstance use across the cohorts to see if the frequency of UDS improves engagement.

Response - Poly substance use data were not available for this study and that has been listed in the limitations

Reference in Main Document – Track changes: Strengths and limitations

Comment 3:

In clinical practice weekly, UDS does not allow for patient autonomy and engagement back into society. The association is too weak and fraught with bias and publication can negatively impact practices in an already marginalized patient population

Response - It is important to note that not all UDS collection events are associated with a physician appointment. Many patients are attending the clinic more often than weekly and can leave samples during the visit to receive medication. So the frequency of urine collection does not add an additional burden to reintegration over and above the burden of supervised ingestion of medication.

Reference in Main Document – Track changes: Introduction

Associate editor comments

Comment 1:

Strengths and Limitations: ‘Strengths and limitations of this study’ should consist of 3-5 bullet points. However, more than 5 points were provided. Kindly modify the provided ‘Strengths and limitations of this study’ to conform with the requirement.

Response: Thank you, the strengths and limitations section has been modified

Comment 2:

Data Sharing Statement: Data Sharing Statement in ScholarOne is different from main document. Please ensure that the Data Sharing Statement in ScholarOne and main document are the same.

Response: Thank you, the data sharing statements have been changed

Comment 3:

Funding Statement: Please complete the funder name in your funding statement in main document as shown in ScholarOne. Please ensure that the award/ grant number in ScholarOne and main document are the same.

Response: Thank you, the funding statement has been changed

Comment 4:

Author Contributions: I have noticed that the name 'Vojtesek, Frank' is included in your author's list. However, upon checking the contributorship statement, I cannot find his name or initial that corresponds to its name. Kindly confirm. Please ensure that the Author Contributions in ScholarOne and main document are the same.

Response: Thank you, this issue is fixed

Comment 5:

References: Reference citations should be cited in ascending order. Please review again the main document and ensure that all references are cited in ascending order.

Response: Thank you, the references are listed in ascending order