BMJ Open

# Exploring goals in treatment for opioid use disorder: Are patients' goals associated with expected treatment outcomes?



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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-044017 |
| Article Type: | Original research |
| Date Submitted by the Author: | 21-Aug-2020 |
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| Keywords: | Adult psychiatry < PSYCHIATRY, Substance misuse < PSYCHIATRY, QUALITATIVE RESEARCH |
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# Exploring goals in treatment for opioid use disorder: Are patients' goals associated with expected treatment outcomes?

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ABSTRACT

Objectives: Existing methods of measuring effectiveness of pharmacological treatment for opioid use disorder (OUD) are highly variable. Therefore, understanding patients' treatment goals is an integral part of patient-centered care. Our objective is to explore whether patients' treatment goals align with a frequently used clinical outcome, opioid abstinence.

Design: Prospective cohort design

Setting and Participants: We collected prospective data from 2,030 participants who were required to be receiving pharmacological treatment for a diagnosis of OUD in order to meet study inclusion criteria. We asked, "What are your goals in treatment?" and used Nvivo software to identify common themes.

Primary outcome measure: Urine drug screens were collected for 3 months post-study enrolment in order to identify abstinence versus ongoing opioid use. We used logistic regression to examine the association between treatment goals and opioid abstinence.

Results: Participants had a mean age of 39.2 years (standard deviation = 10.7), 44% were female, and median duration in treatment was 2.6 years (interquartile range 5.2). Six overarching goals were identified from patient responses, including "stop or taper off of treatment" (68%), "stay or get clean" (37%), and "live a normal life" (14%). Participants reporting the goal "stay or get clean" had lower odds of abstinence at 3 months than those who did not report this goal (OR = 0.73, 95% CI 0.59-0.91, $p$ = 0.005). Although the majority of patients wanted to taper off or stop medication, this goal was not associated with opioid abstinence, nor were any of their other goals.

Conclusions: Patient goals in OUD treatment do not appear to be associated with program measures of outcome (i.e., abstinence from opioids). Future studies are needed to examine outcomes related to patient-reported treatment goals found in our study;

pain management, employment, and stopping/tapering treatment should all be explored.

Strengths and limitations of this study:

- This study is strengthened by its large sample size (2,000 participants) and multisite design.
- Participating clinics follow a harm-reduction approach to treatment and these findings may not generalize to abstinence-based treatment settings.
- The goals and treatment outcomes of patients newly entering treatment may differ from those of patients who have been in treatment longer and may not be captured in this study.

Key words: opioid agonist treatment, patient-centred care, methadone, buprenorphine, treatment goals

## INTRODUCTION

Opioid use disorder (OUD) remains a clinical and public health challenge, with ongoing high rates of opioid use and overdose deaths.[1] Consequently, growing numbers of patients are enrolled in pharmacological treatment for OUD.[2,3] Methadone, a full opioid agonist, and buprenorphine, a partial opioid agonist, are the two most commonly used medications in the management of OUD; they act to reduce cravings and withdrawal, and support abstinence from ongoing opioid use.[4] Evidence from systematic reviews of experimental studies indicates that both medications reduce opioid use.[5,6] However, not all patients have favorable outcomes,[7,8] and patients who continue to use opioids during treatment have a high risk of overdose and death.[9,10]

Better understanding patients' goals in treatment is considered increasingly important within the field of substance use and addiction.[11-13] The now well-known concept of *patient-centered care* was originally coined with the definition of "care that is respectful of, and responsive to, individual patient preferences, needs, and values",[14,15] and is demonstrated to have a significant impact on patients' outcomes and satisfaction in treatment.[16] Increasing attention is being paid to patients' goals and the implementation of patient-centred care principles in addiction treatment.[17]

Identifying core treatment outcomes is an active area of investigation within the field of Addiction Medicine. Unfortunately, there is still significant variability in the outcomes used to evaluate the effectiveness of pharmacological treatment for OUD.[18] How to best measure and assess treatment outcomes remains uncertain, and current practices risk being based upon convenience. Opioid use, measured by urine drug screens (UDS), and retention in treatment are the most commonly used primary outcomes measured in clinical studies and treatment programs;[18] however, it is unknown how well these outcomes are associated with patients' goals in treatment. Personal and social functioning outcomes are, in contrast, much less commonly assessed.[18] As core endpoints and outcome sets for studies of OUD are developed, it is critical to understand which goals in treatment are important to patients and how to best measure them.

In a recent study by Sanger et al., 2020, we used qualitative analysis methods to examine patient-reported treatment goals in a cohort of more than 2,000 patients receiving outpatient pharmacological treatment for OUD.[19] We identified six distinct

goals in treatment from patient responses, including to control cravings or withdrawal, to maintain or stabilize medication dose, to stop or taper off treatment, to "stay or get clean", to manage pain, and to "live a normal life".[19]

The objective of the present study was to explore whether these patient-reported treatment goals are associated with abstinence from opioid use (a frequently measured program outcome). We hypothesized that patient goals related to drug use would be associated with opioid use during treatment; meanwhile, goals unrelated to drug use would have no association with UDS results.

## METHODS

### *Data*

We collected prospective observational data from 2,030 participants recruited from 45 outpatient clinics in the Pharmacogenetics of Opioid Substitution Treatment Response (POST) study. To meet study inclusion criteria, participants were required to be receiving pharmacological treatment (for any length of time) for a diagnosis of OUD, as per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)[20]. No other inclusion or exclusion criteria were applied in order to increase the generalizability of this study. Participants completed face-to-face interviews at study entry to collect information on demographic and clinical characteristics.

At study intake, all participants were asked the open-ended question, "What are your goals in treatment".[19] We used NVivo software QSR International [Americas] Inc., Burlington, Massachusetts, USA) for qualitative analysis to identify common themes from patient answers.[21] We began by reviewing the open-ended question data in Microsoft Excel to minimize typographical errors present in the free text responses and to get a better understanding of the data present. We then imported the data onto the NVivo platform and began cataloguing main ideas, phrases, and patterns into nodes using word and text queries, and a review of the transcribed data. Word and text queries helped us capture the patterns in data and improve analytic accuracy by identifying stemmed variants. This was followed by regular housekeeping of nodes which included the collapsing of related nodes into one node. These steps were completed iteratively, eventually allowing well researched nodes to become themes. Ultimately, we identified six distinct "themes" or "goals" in treatment: 1) to control cravings or withdrawal, 2) to maintain or stabilize medication dose, 3) to stop or taper

off treatment, 4) to "stay or get clean", 5) to manage pain, and 6) to "live a normal life".[19]

We collected the results of UDSs for opioids for three months following study entry to assess treatment outcome. The FaStep Assay (Trimedic Supply Network Ltd, Concord, Ontario, Canada) was used to detect morphine, oxycodone, fentanyl, methadone metabolite, and buprenorphine, as well as other non-opioid substances.[22] UDSs were collected following clinic protocol (typically weekly or biweekly). This study was conducted in accordance with the ethical guidelines of the Hamilton Integrated Research Ethics Board (project ID 4556) and all participants provided informed consent. We report methods and results in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[23]

*Statistical analysis*

We conducted all quantitative analyses using Stata Version 15.1 (StataCorp LP, College Station, TX, USA). We report demographic and clinical data using mean and standard deviation (SD) for normally distributed continuous variables and median with quartiles 1 and 3 or interquartile range (IQR) for skewed data. We report categorical variables as frequency with percentage. We summarize the results of UDSs in three ways: 1) the mean number of UDSs collected; 2) the percentage of opioid-positive UDSs; and 3) abstinence from opioid use, defined as no opioid-positive UDSs during the 3-month time period.

We used logistic regression analysis to examine the association between patient goals in treatment and abstinence from opioid use, adjusting for other important covariates. We constructed a logistic regression model, using the dependent variable abstinence from opioid use throughout the 3 months following study entry. We included the six identified treatment goals in the model and controlled for other factors believed to impact ongoing opioid use in treatment, including age, sex,[24,25] type of treatment (methadone or buprenorphine-naloxone), medication dose,[26] length of time in treatment,[27] and abstinence from opioids at baseline. We also conducted an additional logistic regression to determine whether the number of goals reported by participants was associated with opioid abstinence, as patients who report more treatment needs tend to have more opioid use.[28] Results are reported as odds ratios (OR) with 95% confidence intervals (CI) and associated *p* values. We report the estimates of effect for our main variables of interest (treatment goals) in the results table and describe all variables adjusted for in

a footnote in the table in order to focus solely on the variables of interest to our specific study question. We assessed for multicollinearity using variance inflation factor and examined model diagnostics using the Hosmer-Lemeshow statistic and deviance residuals. We conducted a sensitivity analysis after excluding observations with a deviance residual lower than -2 or higher than 2. Our sample size of 2,030 participants and event rate of more than 1,000 participants abstinent from opioids is adequate, based on the rule of thumb for number of events needed (n = 10) per covariate included in logistic regression analysis.[29]

Missing data were identified and reported for each variable of interest. There were less than 5 cases with missing data for baseline demographic or clinical variables. For 3-month UDS, missing data affected 34 participants (1.7%). Reasons for missing 3-month UDS data included: results not yet available (n = 6), transfer to another clinic (n = 8), treatment failure (n = 10), incarceration (n = 3), completion of treatment (n=2), and other (n = 4), such as hospitalization, moving, or never starting treatment. Due to the low percentage of missing data, all missing data were handled by available case analysis.

## RESULTS

### *Participant characteristics and goals in treatment*

Altogether, 2,030 participants were included in the analyses (Figure 1; Study flow diagram), with a mean age of 39.2 years (SD = 10.7) and 44% were female (Table 1). The majority of participants were receiving treatment with methadone (78.9%) compared to buprenorphine-naloxone (21.1%) and the median length of time in treatment was 2.6 years (IQR 5.2). UDSs collected for the three months of study duration were available for 1,996 participants. Among these participants, 57% were abstinent from opioid use during those 3 months. The most common patient-reported goal was to "stop or taper off treatment" (68%; see Table 1 for all goals). Other goals included to "stay or get clean" (37%), to "live a normal life" (14%), and to control cravings or withdrawal (12%). Most participants (60.2%) reported one treatment goal (mean number of goals = 1.49, SD = 0.67).

### *Association between patients' goals in treatment and 3-month abstinence from opioid use (MAT program goal)*

We examined the association between patient goals and abstinence from opioid use for 3 months following study entry, adjusting

for other characteristics previously shown to be associated with ongoing opioid use (Table 2). Paradoxically, participants reporting the goal "to stay or get clean" had 27% lower odds of abstinence from opioids at 3 months (OR = 0.73, 95% CI 0.59-0.91, $p$ = 0.005), even after adjusting for baseline abstinence from opioid use. No other patient-reported goals in treatment were significantly associated with 3-month abstinence.

Good model fit was assessed using the Hosmer-Lemeshow statistic ($\chi 2$ = 5.93, p = 0.656) and multicollinearity was not a concern (mean VIF 1.19). Using deviance residuals, we detected 14 outliers with deviance residuals greater than an absolute value of 2. We conducted a post-hoc sensitivity analysis removing outliers and found that participants who reported the goal "to control cravings or withdrawal" also had significantly lower odds of opioid abstinence at 3 months (OR = 0. .2, 95% CI 0.54-0.99, $p$ = 0.044; data not shown). There were no other significant changes to the results upon removing outliers.

Finally, the number of goals reported by participants was not significantly associated with 3-month abstinence (data not shown).

## DISCUSSION

In this prospective cohort study, we examined treatment goals reported by more than 2,000 patients receiving pharmacological treatment for OUD to determine their association with the frequently measured treatment outcome, opioid use. Participants reporting the goals to "stay or get clean" and to control cravings or withdrawal were less likely to be abstinent from opioids during the next 3 months of treatment than participants who did not report those goals. Other goals related to termination of treatment, pain or personal or social functioning were not associated with opioid use. These findings suggest that abstinence from opioids, a commonly used treatment outcome measured in clinical trials, does not reflect what patients want out of treatment.

We found that patients who identified goals related to stopping drug use or controlling OUD symptoms had worse outcomes in treatment as measured by UDS. One possible explanation is that patients who were experiencing worse outcomes in treatment or higher severity of illness were more likely to report goals regarding management of substance use symptoms and abstinence from drug use, thus also increasing the likelihood that they experienced ongoing opioid use. Another possibility is that

participants who had achieved abstinence or had improvements in OUD withdrawal symptoms may have been less likely to identify the same goals.

Although the majority of patients wanted to taper off or stop treatment, this goal had no association with abstinence from opioid use. This finding calls into question the rationale for entering and continuing pharmacological treatment while continuing to use opioids for this group of patients. Furthermore, this is a particularly important finding, given that retention in treatment is amongst the most consistently measured outcomes,[18] and guidance around taper and discontinuation of long-term opioid agonist treatments for opioid use disorder is limited.[4,33] Studies examining opioid agonist tapers have identified challenges and risks of poor outcomes[34,35] including withdrawal symptoms, return to drug use, pain, psychiatric symptoms, hospitalization, and death.[36,37] A previous study found that patients' interest in stopping treatment was associated with shorter duration of treatment and lack of concern about relapse to opioid use.[38] This is concerning as one would hope patients planning to stop treatment would be reliably abstinent from opioids. What distinguishes this group of patients who wish to discontinue treatment? Whether some of these patients are mandated to be in treatment is unknown. Better understanding patients' reasons for wanting to stop or taper treatment and examining outcomes for patients who initiate an opioid agonist taper is imperative.

Other patient identified goals in treatment that were not associated with the results of their UDS, included goals around pain management, and the goal "to live a normal life". This suggests that clinicians and researchers may require additional tools to measure outcomes related to those patient-important treatment goals. Tools validated to assess pain in this population include the Brief Pain Inventory[30,31] and social functioning may be examined using the Maudsley Addiction Profile.[32] A more nuanced understanding of specific goals around personal and social functioning, on a population and individual level, is required in order to be able to appropriately assess and address these goals during treatment.

This study has a number of potential limitations. There may be a healthy user/volunteer bias,[39] such that individuals with better outcomes in treatment may have been more likely to participate. Additionally, the goals and treatment outcomes of patients newly entering treatment may differ from those of patients who have been in treatment longer. Patients who may have successfully

achieved their goal of termination of treatment were not captured by this study since they would no longer be on OUD thus not recruited. The findings in this study may not generalize to settings in which opioid agonist medications take on a primarily abstinence-based role in treatment. In Canada, pharmacological treatment for OUD is provided largely in a harm-reduction model, in which retention in treatment is not contingent on abstinence from opioids or non-opioid substances. This study did not measure patient's satisfaction or perception of treatment success or perception of meeting their goals. Future studies that examine patient satisfaction in treatment may wish to determine whether perception of treatment success correlates with program-measured outcomes such as opioid abstinence.

## CONCLUSION

Patients report a number of different goals in their treatment for OUD, which are not associated with traditional goals of treatment programs and outcomes measured in clinical settings (abstinence from opioid use measured by UDS). We found that patients who identified goals related to stopping drug use or controlling OUD symptoms were more likely to have ongoing opioid use. However, goals unrelated to drug use carried no significant association with opioid use status. Patients reporting the goal of wanting to stop treatment were no more likely to be abstinent from opioids. The patient-identified goals to manage pain or "live a normal life" had no association with ongoing opioid use. Future studies are needed to examine outcomes related to the goals in treatment identified in our study. Are these goals being met in treatment? For example, do patients feel their pain is well managed? Do they achieve employment? Can they achieve the goal of stopping treatment without adverse consequences? As core outcome sets are developed, patient-important outcomes remain essential to consider and may help with implementing patient-centered approaches to treatment.

## ACKNOWLEDGMENTS

We would like to thank the Pharmacogenetics of Opioid Substitution Treatment Response (POST) study participants for their time and contributions, without which this study would not be possible.

## Authors' contributions

TR, LN, BP, NS, BBD, and ZS are responsible for the study concept and design. TR, BP, LT and ZS developed the methods and data analysis. TR conducted quantitative analysis and BP

conducted qualitative analysis. TR wrote the first draft of the manuscript, and TR, LN, BP, DBC, NS, BBD, DCM, LR, AW, LT, and ZS, contributed to writing and critically revising the final manuscript. All authors reviewed and approved the final manuscript.

## Role of funding source

This study was supported by research grants from the Canadian Institutes for Health Research (grant numbers PJT-156306 and SHI-155404). The funding bodies had no role in the design, analysis, interpretation, or publication of results.

## Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

## Declaration of interests

Dr. Marsh reports Salary income as Chief Medical Director, Canadian Addiction Treatment Centres and as Associate Dean Research, Innovation and International Relations, Northern Ontario School of Medicine. The other study authors declare no conflicts of interest.

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**Table 1.** Characteristics of participants at study entry (N = 2,030).

| Characteristic | Statistic |
|---|---|
| **Demographic and clinical** | |
| Age in years; mean (SD) | 39.2 (10.7) |
| Female sex [a]; *n* (%) | 894 (44.1) |
| Type of treatment; *n* (%) | |
| Methadone | 1601 (78.9) |
| Buprenorphine-naloxone | 429 (21.1) |
| Dose in mg/day; mean (SD) | |
| Methadone | 70.5 (41.4) |
| Buprenorphine-naloxone | 12.0 (6.7) |
| Years in treatment [a]; median (IQR) | 2.6 (5.2) |
| Abstinence from opioid use at baseline [b]; *n* (%) | 646 (31.9) |
| Number of opioid urine drug screens at 3 months [c]; mean (SD) | 12.6 (5.3) |
| Median percentage of opioid-positive urine drug screens at 3 months [c]; median (Q1, Q3) | 0 (0, 20) |
| Abstinence from opioid use at 3 months [c]; *n* (%) | 1,127 (56.5) |
| **Patient-reported goals in treatment [d]** | |
| Number of goals reported; *n* (%) | |
| One | 1222 (60.2%) |
| Two | 643 (31.7%) |
| Three | 150 (7.4%) |
| Four | 13 (0.64%) |
| Five | 2 (0.1%) |
| Control cravings/withdrawal | 247 (12.17%) |

| | |
|---|---|
| Maintain or stabilize medication dose | 122 (6.01%) |
| "Live a normal life" | 283 (13.94%) |
| Manage pain | 240 (11.82%) |
| "Stay or get clean" | 742 (36.55%) |
| Stop or taper off treatment | 1386 (68.28%) |

SD = Standard Deviation, Q1 = 25th percentile, Q3 = 75th percentile

[a] Data available for 2,029 participants.

[b] Data available for 2,028 participants.

[c] Data available for 1,996 participants (missing for 34 participants).

[d] Percentages sum to more than 100% as patients could report multiple goals in treatment.

**Table 2.** Multivariable model of the association between patient goals and abstinence from opioid use for 3 months following study entry.

| | ***Complete case analysis*** [a] **(n = 1, 994** [b]**)** | | | ***Sensitivity analysis excluding outliers*** **(n = 1,980)** [a,c] | | |
|---|---|---|---|---|---|---|
| **Covariate** | **OR** | **95% CI** | ***p*** | **OR** | **95% CI** | ***p*** |
| Control cravings/withdrawal | 0.76 | 0.56, 1.03 | 0.078 | 0.73 | 0.54, 0.99 | 0.044 |
| Maintain or stabilize medication dose | 1.15 | 0.74, 1.79 | 0.523 | 1.24 | 0.79, 1.95 | 0.354 |
| "Live a normal life" | 1.02 | 0.77, 1.35 | 0.879 | 0.98 | 0.74, 1.31 | 0.902 |
| Manage pain | 1.0 | 0.73, 1.36 | 0.976 | 0.96 | 0.70, 1.32 | 0.806 |
| "Stay or get clean" | 0.73 | 0.59, 0.91 | 0.005 | 0.70 | 0.56, 0.87 | 0.001 |
| Stop or taper off treatment | 1.0 | 0.80, 1.27 | 0.974 | 1.01 | 0.80, 1.27 | 0.954 |

OR = Odds Ratio, CI = Confidence Interval

Variance inflation factor = 1.19

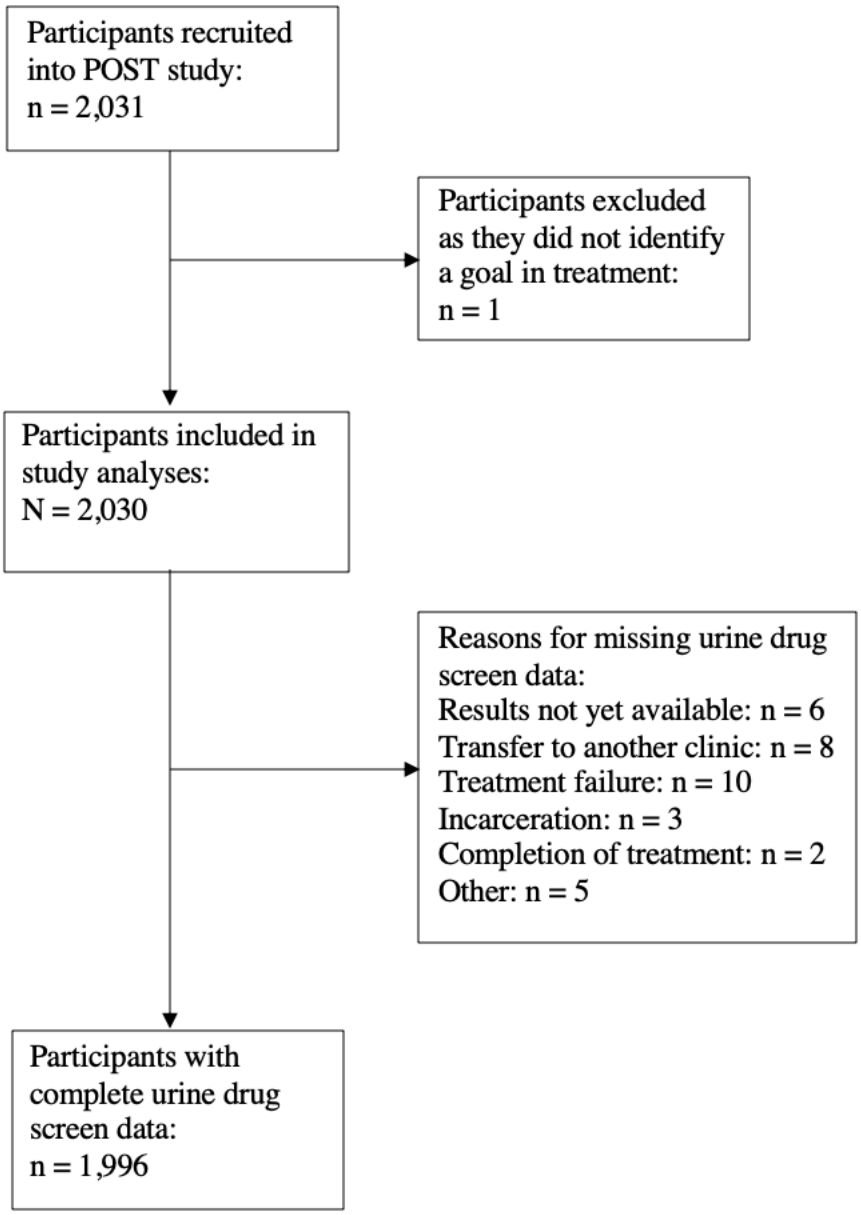
Hosmer-Lemeshow $\chi^2$ 5.93, $p$ = 0.656

[a] Model is adjusted for age, sex, type of treatment (methadone or buprenorphine-naloxone), dose, length of time in treatment, and opioid abstinence at baseline.

[b] Participants with missing data in any of the included covariates are excluded due to complete case analysis (missing urine drug screen data: n = 36, missing sex: n = 1, missing length of time in treatment: n =1).

[c] Excluding 14 outliers detected using deviance residuals less than -2 from the analysis

**Figure 1**. Study flow diagram.



STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation | Included on page: |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Abstract |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Abstract |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 (intro, paragraphs 1-3) |
| Objectives | 3 | State specific objectives, including any pre-specified hypotheses | 3 (intro, paragraph 5) |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 3-4 (Methods, Data section) |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 3-4 (Methods, Data section) |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 3 (Methods, paragraph 1, 3) |
| | | *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls | |
| | | *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed | |
| | | *Case-control study*—For matched studies, give matching criteria and the number of controls per case | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4 (Statistical analysis, paragraph 2) |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 4 (Methods) |

| | | | |
|---|---|---|---|
| Bias | 9 | Describe any efforts to address potential sources of bias | Methods (Data), Limitations (page 7) |
| Study size | 10 | Explain how the study size was arrived at | Figure 1 Study Flow Diagram |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Methods, Statistical analysis page 4 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Methods, Statistical analysis page 4 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | |
| | | (*c*) Explain how missing data were addressed | Page 5 first paragraph |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed | |
| | | *Case-control study*—If applicable, explain how matching of cases and controls was addressed | |
| | | *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | |
| Continued on next page | | | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Study flow diagram Figure 1 |
| | | (b) Give reasons for non-participation at each stage | Study flow diagram Figure 1 |
| | | (c) Consider use of a flow diagram | Study flow diagram Figure 1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Table 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Table 1 |

| | | | |
|---|---|---|---|
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | Table 1 |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | Table 1 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Table 2 |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Results page 5, paragraph 3 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Discussion page 6 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Discussion page 7 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Discussion page 6 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Discussion page 7 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Title page |

Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
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| | | (*e*) Describe any sensitivity analyses |

Continued on next page

**Results**

| | | | | | |
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| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | | | |
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BMJ Open

# Are patients' goals in treatment associated with expected treatment outcomes? Findings from a mixed-methods study on outpatient pharmacological treatment for opioid use disorder.



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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-044017.R1 |
| Article Type: | Original research |
| Date Submitted by the Author: | 12-Nov-2020 |
| Complete List of Authors: | Rosic, Tea; McMaster University, Department of Psychiatry and Behavioral Neurosciences; McMaster University, Department of Health Research, Evidence and Impact<br>Naji, Leen; McMaster University, Department of Family Medicine, McMaster University, Hamilton, Ontario, Canada<br>Panesar, Balpreet; McMaster University, Neurosciences Graduate Program, McMaster University, Hamilton, Ontario, Canada<br>Chai, Darren; McMaster University, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada<br>Sanger, Nitika; McMaster University, Medical Science Gradaute Program<br>Dennis, Brittany; McMaster University, Department of Medicine, McMaster University, Hamilton, Ontario, Canada: 1280 Main St W, Hamilton, ON L8S 4L8<br>Marsh, David; Northern Ontario School of Medicine,<br>Rieb, Launette; University of British Columbia Faculty of Graduate Studies<br>Worster, Andrew; McMaster University, Division of Emergency Medicine<br>Thabane, Lehana ; McMaster University, Clinical Epidemiology & Biostatistics<br>Samaan, Zainab; McMaster University, Psychiatry and Behavioral Neurosciences |
| Primary Subject Heading: | Addiction |
| Secondary Subject Heading: | Patient-centred medicine, Addiction, Qualitative research |
| Keywords: | Adult psychiatry < PSYCHIATRY, Substance misuse < PSYCHIATRY, QUALITATIVE RESEARCH |
| | |

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# Are patients' goals in treatment associated with expected treatment outcomes? Findings from a mixed-methods study on outpatient pharmacological treatment for opioid use disorder.

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ABSTRACT

Objectives: Existing methods of measuring effectiveness of pharmacological treatment for opioid use disorder (OUD) are highly variable. Therefore, understanding patients' treatment goals is an integral part of patient-centered care. Our objective is to explore whether patients' treatment goals align with a frequently used clinical outcome, opioid abstinence.

Design: Triangulation mixed-methods design

Setting and Participants: We collected prospective data from 2,030 participants who were receiving methadone or buprenorphine-naloxone treatment for a diagnosis of OUD in order to meet study inclusion criteria. Participants were recruited from 45 centrally-managed outpatient opioid agonist therapy clinics in Ontario, Canada. At study entry, we asked, "What are your goals in treatment?" and used Nvivo software to identify common themes.

Primary outcome measure: Urine drug screens (UDS) were collected for 3 months post-study enrolment in order to identify abstinence versus ongoing opioid use (mean number of UDS over 3 months = 12.6, standard deviation (SD) = 5.3)). We used logistic regression to examine the association between treatment goals and opioid abstinence.

Results: Participants had a mean age of 39.2 years (SD = 10.7), 44% were female, and median duration in treatment was 2.6 years (interquartile range 5.2). Six overarching goals were identified from patient responses, including "stop or taper off of treatment" (68%), "stay or get clean" (37%), and "live a normal life" (14%). Participants reporting the goal "stay or get clean" had lower odds of abstinence at 3 months than those who did not report this goal (OR = 0.73, 95% CI 0.59-0.91, $p$ = 0.005). Although the majority of patients wanted to taper off or stop medication, this goal was not associated with opioid abstinence, nor were any of their other goals.

Conclusions: Patient goals in OUD treatment do not appear to be associated with program measures of outcome (i.e., abstinence from opioids). Future studies are needed to examine outcomes related to patient-reported treatment goals found in our study; pain management, employment, and stopping/tapering treatment should all be explored.

Strengths and limitations of this study:

- This study is strengthened by its large sample size (2,000 participants) and multisite design.
- Participating clinics follow a harm-reduction approach to treatment and these findings may not generalize to abstinence-based treatment settings.
- The goals and treatment outcomes of patients newly entering treatment may differ from those of patients who have been in treatment longer and may not be captured in this study.

Key words: opioid agonist treatment, patient-centred care, methadone, buprenorphine, treatment goals

## INTRODUCTION

Opioid use disorder (OUD) remains a clinical and public health challenge, with ongoing high rates of opioid use and overdose deaths.[1] Consequently, growing numbers of patients are enrolled in pharmacological treatment for OUD.[2,3] Methadone, a full opioid agonist, and buprenorphine, a partial opioid agonist, are the two most commonly used medications in the management of OUD; they act to reduce cravings and withdrawal, and support abstinence from ongoing opioid use.[4] Evidence from systematic reviews of experimental studies indicates that both medications reduce opioid use.[5,6] However, not all patients have favorable outcomes,[7,8] and patients who continue to use opioids during treatment have a high risk of overdose and death.[9,10] Other treatments, including heroin-assisted treatment, are available in some jurisdictions for patients who have limited response to treatment with first-line medications.[11]

Better understanding patients' goals in treatment is considered increasingly important within the field of substance use and addiction.[12-14] The now well-known concept of *patient-centered care* was originally coined with the definition of "care that is respectful of, and responsive to, individual patient preferences, needs, and values",[15,16] and is demonstrated to have a significant impact on patients' outcomes and satisfaction in treatment.[17] Increasing attention is being paid to patients' goals and the implementation of patient-centred care principles in addiction treatment.[18]

Identifying core treatment outcomes is an active area of investigation within the field of Addiction Medicine.[19] Unfortunately, there is still significant variability in the outcomes used to evaluate the effectiveness of pharmacological treatment for OUD.[20, 21] How to best measure and assess treatment outcomes remains uncertain, and current practices risk being based upon convenience. Opioid use, measured by urine drug screens (UDS), and retention in treatment are the most commonly used primary outcomes measured in clinical studies and treatment programs;[21] however, it is unknown how well these outcomes are associated with patients' goals in treatment. Personal and social functioning outcomes are, in contrast, much less commonly assessed.[21] As core endpoints and outcome sets for studies of OUD are developed, it is critical to understand which goals in treatment are important to patients and how to best measure them.

In a recent study by Sanger et al., 2020, we used qualitative analysis methods to examine patient-reported treatment goals in a cohort of more than 2,000 patients receiving outpatient pharmacological treatment for OUD.[22] We identified six distinct goals in treatment from patient responses, including to control cravings or withdrawal, to maintain or stabilize medication dose, to stop or taper off treatment, to "stay or get clean", to manage pain, and to "live a normal life".[22]

The objective of the present study was to explore whether these patient-reported treatment goals are associated with abstinence from opioid use (a frequently measured program outcome). We hypothesized that patient goals related to drug use would be associated with opioid use during treatment; meanwhile, goals unrelated to drug use would have no association with UDS results.

## METHODS

### *Data*

We collected prospective observational data from 2,030 participants recruited from 45 outpatient clinics in the Pharmacogenetics of Opioid Substitution Treatment Response (POST) study. To meet study inclusion criteria, participants were required to be at least 16 years of age and receiving pharmacological treatment with methadone or buprenorphine-naloxone (for any length of time) for a diagnosis of OUD, as per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).[23] The diagnosis of OUD was made by treating

physicians according to DSM-5 criteria and is an eligibility criterion for treatment entry and clinical follow up at the outpatient clinics included in this study. No other inclusion or exclusion criteria were applied in order to increase the generalizability of this study. Participants completed face-to-face interviews at study entry to collect information on demographic and clinical characteristics.

We used a triangulation mixed-methods design to combine quantitative and qualitative data collection, where both quantitative and qualitative data were collected within one study instrument using closed- and open-ended questions.[24,25] At study intake, participants were interviewed by trained research staff to obtain information on sociodemographic and clinical information, medical history, and substance use history. Research staff have a background in addiction research, as they have previously participated in recruitment of participants for a study investigating genetic influences on methadone treatment.[26] Their experience allowed for familiarity of addiction related terms used in interview responses, but they were not known to the participants of this research study. Study interviews were conducted in-person at the CATC. The interview data used in this study is from participants recruited from May 2018 until August 2019. During the interview, all participants who met the inclusion and exclusion criteria above were asked the open-ended question, "What are your goals in treatment". Details regarding the study settings and data collection are outlined in a previous study looking at OUD-related patient important outcomes.[22] Verbal responses, in their entirety, were transcribed by research staff word-for-word in online anonymized records, where each participant was given an anonymized record number.

We collected the results of UDSs for opioids for each participant for three months following study entry to assess treatment outcome. The FaStep Assay (Trimedic Supply Network Ltd, Concord, Ontario, Canada) was used to detect morphine, oxycodone, fentanyl, methadone metabolite, and buprenorphine, as well as other non-opioid substances.[27] Though other methods may be used to assess ongoing opioid use during treatment, such as saliva and hair tests, as well as self-report,[28] UDSs are collected as part of routine clinical protocol in the clinics participating in this study and are a recommended method of assessment based on Canadian Guidelines.[4] UDSs were collected following clinic protocol (typically weekly or biweekly). For each participant, we calculated the percentage of opioid-positive UDSs by dividing the number of opioid-positive urines

by the number of urine samples taken. Abstinence from opioids was selected as our primary study outcome as it is a routinely measured treatment outcome in both clinical practice and research studies.

Another commonly studied treatment outcome, retention in treatment, was not formally assessed in the present study for two reasons. First, treatment retention is not equivalent to the duration of time enrolled in this study (as our study used a naturalistic design and enrolled patients in various stages of their treatment). Second, with the exception of patients who have entered treatment for the first time, there exists some uncertainty in defining treatment retention because patients frequently enter and discontinue treatment at various points in their course of illness. Instead, we asked participants to report their length of time enrolled in this treatment episode (as a proxy for treatment retention) and adjusted all study analyses for length of time in treatment.

This study was reviewed and approved by the Hamilton Integrated Research Ethics Board (project ID 4556) and conducted in accordance with its ethical guidelines. We report methods and quantitative results in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[29]

*Qualitative analysis*

The qualitative approach used to analyze the data was data-driven thematic analysis.[30] We began by familiarizing ourselves with the data through active, repeated reading of the interview responses and began to recognize emerging patterns. This phase of data familiarization also allowed us to minimize typographical errors present in the free text responses. We began phase two by generating initial codes using NVivo software QSR International [Americas] Inc., Burlington, Massachusetts, USA) for qualitative analysis to identify common themes from patient answers.[31] We began cataloguing main ideas, phrases, and patterns into meaningful nodes using word and text queries, and a review of the transcribed data. Word and text queries helped us capture the patterns in data and improve analytic accuracy by identifying stemmed variants. Each data item was given equal attention and in addition to text and word queries, key phrases were tagged within each data item. This phase is characterized by the generation of a codebook that provided specific definitions of the key phrases, words and patterns. The next

phase consisted of the labelling of some nodes as themes and the collapsing of related nodes into one node, eventually being labelled as a themes or sub-themes. The final phase consisted of a review of identified themes and resultant reworking of themes to better establish coherent patterns within each theme. Defining and refining of each theme followed this phase, where patterns and content were considered before choosing relevant and reflective theme names.[30,32] To increase rigour in our analysis we used investigator triangulation, where phases concerning the generation of themes involved the consultation of four investigators to ensure incorporation of diverse perspectives. This was reflected in the iterative review of nodes and patterns, where meaningfulness of coding was discussed and was reassessed at every identified phase. We report qualitative methods and results in accordance with the Standards of Reporting Qualitative Research (SRQR).[33]

*Quantitative analysis*

We conducted all quantitative analyses using Stata Version 15.1 (StataCorp LP, College Station, TX, USA). We report demographic and clinical data using mean and standard deviation (SD) for normally distributed continuous variables and median with quartiles 1 and 3 or interquartile range (IQR) for skewed data. We report categorical variables as frequency with percentage. We summarize the results of UDSs in three ways: 1) the mean number of UDSs collected; 2) the percentage of opioid-positive UDSs; and 3) abstinence from opioid use, defined as no opioid-positive UDSs during the 3-month time period.

We used logistic regression analysis to examine the association between patient goals in treatment and abstinence from opioid use, adjusting for other important covariates. We constructed a logistic regression model, using the dependent variable abstinence from opioid use throughout the 3 months following study entry. We included the six identified treatment goals in the model and controlled for other factors believed to impact ongoing opioid use in treatment, including age, sex,[34,35] type of treatment (methadone or buprenorphine-naloxone), medication dose,[36] length of time in treatment,[37] and abstinence from opioids at baseline. We also conducted an additional logistic regression to determine whether the number of goals reported by participants was associated with opioid abstinence, as patients who report more treatment needs tend to have more opioid use.[38] Results are reported as odds ratios (OR) with 95% confidence intervals (CI) and associated *p* values. We report the estimates

of effect for our main variables of interest (treatment goals) in the results table and describe all variables adjusted for in a footnote in the table in order to focus solely on the variables of interest to our specific study question. We assessed for multicollinearity using variance inflation factor and examined model diagnostics using the Hosmer-Lemeshow statistic and deviance residuals. We conducted a sensitivity analysis after excluding observations with a deviance residual lower than -2 or higher than 2. Our sample size of 2,030 participants and event rate of more than 1,000 participants abstinent from opioids is adequate, based on the rule of thumb for number of events needed (n = 10) per covariate included in logistic regression analysis.[39]

Missing data were identified and reported for each variable of interest. There were less than 5 cases with missing data for baseline demographic or clinical variables. For 3-month UDS, missing data affected 34 participants (1.7%). Reasons for missing 3-month UDS data included: results not yet available (n = 6), transfer to another clinic (n = 8), treatment failure (n = 10), incarceration (n = 3), completion of treatment (n=2), and other (n = 4), such as hospitalization, moving, or never starting treatment. Due to the low percentage of missing data, all missing data were handled by available case analysis.

**Patient and Public Involvement**

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

*Participant characteristics and goals in treatment*

Altogether, 2,030 participants were included in the analyses (Figure 1; Study flow diagram), with a mean age of 39.2 years (SD = 10.7) and 44% were female (Table 1). The majority of participants were receiving treatment with methadone (78.9%) compared to buprenorphine-naloxone (21.1%) and the median length of time in treatment was 2.6 years (IQR 5.2). UDSs collected for the three months of study duration were available for 1,996 participants. Among these participants, 57% were abstinent from opioid use during those 3 months. Ultimately, we identified six distinct "themes" or "goals" in treatment: 1) to control cravings or withdrawal, 2) to maintain or stabilize medication dose, 3) to stop or taper off treatment, 4) to "stay or get

clean", 5) to manage pain, and 6) to "live a normal life", as presented by our previous paper looking at patient important outcomes in the OUD population receiving MAT.[22] The "control cravings or withdrawal" theme consisted of participants responses stating they would like to avoid withdrawal or control their cravings. Participant responses grouped in the second theme of "no changes in treatment" were made up of responses indicating that they wanted to maintain OSAT doses, stabilize their OSAT dose, or did not have any reported goals. The third goal to "stop OSAT treatment" had goals to stop treatment completely, to not be dependent on OSAT, to taper off, or reduce dose. Participant goals such as wanting to get clean, stay clean, achieve abstinence, or achieve sobriety from all drugs were included in the fourth goal of "avoiding illicit drugs". The fifth theme of "pain management" either mentioned chronic pain, or pain management in general. The sixth theme of "living a normal life" consisted of responses such as wanting a stable life, normal life, to get qualifications related to education, job or work, to achieve good mental health, or wanting to support their family.[22]

The most common patient-reported goal was to "stop or taper off treatment" (68%; see Table 1 for all goals). Other goals included to "stay or get clean" (37%), to "live a normal life" (14%), and to control cravings or withdrawal (12%). Most participants (60.2%) reported one treatment goal (mean number of goals = 1.49, SD = 0.67).

*Association between patients' goals in treatment and 3-month abstinence from opioid use (MAT program goal)*

We examined the association between patient goals and abstinence from opioid use for 3 months following study entry, adjusting for other characteristics previously shown to be associated with ongoing opioid use (Table 2). Paradoxically, participants reporting the goal "to stay or get clean" had 27% lower odds of abstinence from opioids at 3 months (OR = 0.73, 95% CI 0.59-0.91, $p$ = 0.005), even after adjusting for baseline abstinence from opioid use. No other patient-reported goals in treatment were significantly associated with 3-month abstinence.

Good model fit was assessed using the Hosmer-Lemeshow statistic ($\chi 2$ = 5.93, p = 0.656) and multicollinearity was not a concern (mean VIF 1.19). Using deviance residuals, we detected 14 outliers with deviance residuals greater than an absolute value of 2. We conducted a post-hoc sensitivity analysis removing outliers and found that participants who reported the goal "to control cravings or withdrawal" also had significantly lower odds of opioid abstinence at 3 months (OR = 0.73, 95% CI 0.54-0.99, $p$ = 0.044; Supplementary Table 1). There were no other significant changes to the results upon removing outliers.

Finally, we examined the association between number of reported goals and abstinence from opioid use for 3 months (Supplementary Table 2). As compared to reporting one goal in treatment, reporting two goals was not associated with opioid use (OR = 0.93, 95% CI = 0.75, 1.15, $p$ = 0.497), however reporting three or more goals may be associated with lower odds of abstinence from opioids (OR = 0.70, 95% CI = 0.49, 1.0, $p$ = 0.049).

## DISCUSSION

In this mixed-methods study, we examined treatment goals reported by more than 2,000 patients receiving pharmacological treatment for OUD to determine their association with the frequently measured treatment outcome, opioid use. Participants reporting the goals to "stay or get clean" and to control cravings or withdrawal were less likely to be abstinent from opioids during the next 3 months of treatment than participants who did not report those goals. Other goals related to termination of treatment, pain or personal or social functioning were not associated with opioid use. These findings suggest that abstinence from opioids, a commonly used treatment outcome measured in clinical trials, does not reflect what patients want out of treatment, and raises questions about the alignment between treatment outcomes and patient goals.[40]

We found that patients who identified goals related to stopping drug use or controlling OUD symptoms had worse outcomes in treatment as measured by UDS. There is a rich literature examining the apparent contradiction between abstinence-related goals and subsequent drug-taking behaviors. This is in essence the focus of motivational interviewing[41] in which clinicians help patients develop motivation through recognizing discrepancies between their current situation and their goals, shifting the balance towards change.[42] One possible explanation is that patients who were experiencing worse outcomes in treatment or higher severity of illness were more likely to report goals regarding management of substance use symptoms and abstinence from drug use, thus also increasing the likelihood that they experienced ongoing opioid use. Another possibility is that participants who had achieved abstinence or had improvements in OUD withdrawal symptoms may have been less likely to identify the same goals. Nonetheless, exploring why patients wishing to abstain from opioid use are not achieving this goal is an area requiring further study. Beyond quantitatively examining factors associated with ongoing substance use, previous qualitative studies that explore patient perceptions of barriers and

facilitators to achieving abstinence are illuminating and may inform future interventions and study.[43-45]

Although the majority of patients wanted to taper off or stop treatment, this goal had no association with abstinence from opioid use. One possible explanation is that participants may have been unhappy with treatment and therefore non-adherent. Factors associated with non-adherence to opioid agonist treatments have been previously studied.[46-49] There is a vast literature on factors affecting patient adherence to treatment in general and, notably, no single explanation sufficiently accounts for variation in adherence.[50] Authors in this field have suggested considering the patient's experience of illness and its meaning as important factors to study in understanding adherence to treatment.[50, 51] This finding calls into question the rationale for entering and continuing pharmacological treatment while continuing to use opioids for this group of patients. Furthermore, this is a particularly important finding, given that retention in treatment is amongst the most consistently measured outcomes,[19] and guidance around taper and discontinuation of long-term opioid agonist treatments for opioid use disorder is limited.[4,52] Studies examining opioid agonist tapers have identified challenges and risks of poor outcomes[53,54] including withdrawal symptoms, return to drug use, pain, psychiatric symptoms, hospitalization, and death.[55,56] A previous study found that patients' interest in stopping treatment was associated with shorter duration of treatment and lack of concern about relapse to opioid use.[57] This is concerning as one would hope patients planning to stop treatment would be reliably abstinent from opioids. What distinguishes this group of patients who wish to discontinue treatment? Whether some of these patients are mandated to be in treatment is unknown. Better understanding patients' reasons for wanting to stop or taper treatment and examining outcomes for patients who initiate an opioid agonist taper is imperative.

Other patient identified goals in treatment that were not associated with the results of their UDS, included goals around pain management, and the goal "to live a normal life". This suggests that clinicians and researchers may require additional tools to measure outcomes related to those patient-important treatment goals. Tools validated to assess pain in this population include the Brief Pain Inventory[58,59] and social functioning may be examined using the Maudsley Addiction Profile.[60] A more nuanced understanding of specific goals around personal and social functioning, on a population and individual level, is required in order to be able to appropriately assess

and address these goals during treatment. Overall, our finding that results of UDSs are not associated with all patient goals in treatment is expected as UDSs results would not be expected to be a proxy for all of the different goals. However, this study adds evidence to the notion that traditional metrics of success in opioid use disorder treatment are insufficient in isolation. It is important to note that although patient goals appear to have limited predictive value on opioid use during treatment, this does not imply that clinicians should not ask patients about their treatment goals. It is not uncommon that patients have goals that are not achieved in treatment (e.g., weight loss, increased physical activity) and this does not mean that clinicians or patients should give up on these goals or should not enquire about them. Rather, we must consider how well traditional metrics of treatment success align with desired treatment outcomes for all stakeholders, especially patients, and consider additional ways to evaluate and improve treatment success based on patients' self-reported goals.

Finally, in a previous paper, we examined group differences between participants selecting each treatment goal.[22] Females were more likely to report the goal of stopping treatment. Older age, first exposure to opioids through physician prescription, and unemployment were all associated with greater odds of reporting goals related to pain management.[22] These findings indicated that, unsurprisingly, patients' characteristics are associated with their treatment goals and may help to guide focused questioning and evaluation of patients' goals in treatment.

This study has a number of potential limitations. First, this study interprets and summarizes the patients' narrative when expressing their goals in treatment using qualitative methods; however, this interpretation carries limitations related to the potential influence social desirability bias and the influence of contextual factors on patients' responses that have not been explored in this study. Though beyond the scope of this paper, sociological approaches to qualitative analysis include critical appraisal of the circumstances of the participant and the context in which statements are expressed. Furthermore, there may be a healthy user/volunteer bias,[61] such that individuals with better outcomes in treatment may have been more likely to participate. Additionally, the goals and treatment outcomes of patients newly entering treatment may differ from those of patients who have been in treatment longer. Patients who may have successfully achieved their goal of termination of treatment were not captured by this study since they would no

longer be on OUD thus not recruited. The findings in this study may not generalize to settings in which opioid agonist medications take on a primarily abstinence-based role in treatment. In Canada, pharmacological treatment for OUD is provided largely in a harm-reduction model, in which retention in treatment is not contingent on abstinence from opioids or non-opioid substances. This study did not measure patient's satisfaction or perception of treatment success or perception of meeting their goals. Future studies that examine patient satisfaction in treatment may wish to determine whether perception of treatment success correlates with program-measured outcomes such as opioid abstinence.

## CONCLUSION

Patients report a number of different goals in their treatment for OUD, which are not associated with traditional goals of treatment programs and outcomes measured in clinical settings (abstinence from opioid use measured by UDS). We found that patients who identified goals related to stopping drug use or controlling OUD symptoms were more likely to have ongoing opioid use. However, goals unrelated to drug use carried no significant association with opioid use status. Patients reporting the goal of wanting to stop treatment were no more likely to be abstinent from opioids. The patient-identified goals to manage pain or "live a normal life" had no association with ongoing opioid use. Future studies are needed to examine outcomes related to the goals in treatment identified in our study. Are these goals being met in treatment? For example, do patients feel their pain is well managed? Do they achieve employment? Can they achieve the goal of stopping treatment without adverse consequences? As core outcome sets are developed, patient-important outcomes remain essential to consider and may help with implementing patient-centered approaches to treatment.

## ACKNOWLEDGMENTS

We would like to thank the Pharmacogenetics of Opioid Substitution Treatment Response (POST) study participants for their time and contributions, without which this study would not be possible.

## Authors' contributions

TR, LN, BP, NS, BBD, and ZS are responsible for the study concept and design. TR, BP, LT and ZS developed the methods and data analysis. TR conducted quantitative analysis and BP conducted qualitative analysis. TR wrote the first draft of the

manuscript, and TR, LN, BP, DBC, NS, BBD, DCM, LR, AW, LT, and ZS, contributed to writing and critically revising the final manuscript. All authors reviewed and approved the final manuscript.

**Data availability**

Data are available upon reasonable request

**Role of funding source**

This study was supported by research grants from the Canadian Institutes for Health Research (grant numbers PJT-156306 and SHI-155404). The funding bodies had no role in the design, analysis, interpretation, or publication of results.

**Declaration of interests**

Dr. Marsh reports Salary income as Chief Medical Director, Canadian Addiction Treatment Centres and as Associate Dean Research, Innovation and International Relations, Northern Ontario School of Medicine. The other study authors declare no conflicts of interest.

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**Table 1.** Characteristics of participants at study entry (N = 2,030).

| Characteristic | Statistic |
|---|---|
| **Demographic and clinical** | |
| Age in years; mean (SD) | 39.2 (10.7) |
| Female sex [a]; *n* (%) | 894 (44.1) |
| Type of treatment; *n* (%) | |
| Methadone | 1601 (78.9) |
| Buprenorphine-naloxone | 429 (21.1) |
| Dose in mg/day; mean (SD) | |
| Methadone | 70.5 (41.4) |
| Buprenorphine-naloxone | 12.0 (6.7) |
| Years in treatment [a]; median (IQR) | 2.6 (5.2) |
| Abstinence from opioid use at baseline [b]; *n* (%) | 646 (31.9) |
| Number of opioid urine drug screens at 3 months [c]; mean (SD) | 12.6 (5.3) |
| Median percentage of opioid-positive urine drug screens at 3 months [c]; median (Q1, Q3) | 0 (0, 20) |
| Abstinence from opioid use at 3 months [c]; *n* (%) | 1,127 (56.5) |
| **Patient-reported goals in treatment [d]** | |
| Number of goals reported; *n* (%) | |
| One | 1222 (60.2%) |
| Two | 643 (31.7%) |
| Three | 150 (7.4%) |
| Four | 13 (0.64%) |
| Five | 2 (0.1%) |
| Control cravings/withdrawal | 247 (12.17%) |

| | |
|---|---|
| Maintain or stabilize medication dose | 122 (6.01%) |
| "Live a normal life" | 283 (13.94%) |
| Manage pain | 240 (11.82%) |
| "Stay or get clean" | 742 (36.55%) |
| Stop or taper off treatment | 1386 (68.28%) |

SD = Standard Deviation, Q1 = 25th percentile, Q3 = 75th percentile

[a] Data available for 2,029 participants.

[b] Data available for 2,028 participants.

[c] Data available for 1,996 participants (missing for 34 participants).

[d] Percentages sum to more than 100% as patients could report multiple goals in treatment.

**Table 2.** Multivariable model of the association between patient goals and abstinence from opioid use for 3 months following study entry.

| | ***Complete case analysis*** [a] **(n = 1, 994** [b]**)** | | | ***Sensitivity analysis excluding outliers*** **(n = 1,980)** [a,c] | | |
|---|---|---|---|---|---|---|
| **Covariate** | **OR** | **95% CI** | ***p*** | **OR** | **95% CI** | ***p*** |
| Control cravings/withdrawal | 0.76 | 0.56, 1.03 | 0.078 | 0.73 | 0.54, 0.99 | 0.044 |
| Maintain or stabilize medication dose | 1.15 | 0.74, 1.79 | 0.523 | 1.24 | 0.79, 1.95 | 0.354 |
| "Live a normal life" | 1.02 | 0.77, 1.35 | 0.879 | 0.98 | 0.74, 1.31 | 0.902 |
| Manage pain | 1.0 | 0.73, 1.36 | 0.976 | 0.96 | 0.70, 1.32 | 0.806 |
| "Stay or get clean" | 0.73 | 0.59, 0.91 | 0.005 | 0.70 | 0.56, 0.87 | 0.001 |
| Stop or taper off treatment | 1.0 | 0.80, 1.27 | 0.974 | 1.01 | 0.80, 1.27 | 0.954 |

OR = Odds Ratio, CI = Confidence Interval

Variance inflation factor = 1.19

Hosmer-Lemeshow $\chi^2$ 5.93, $p$ = 0.656

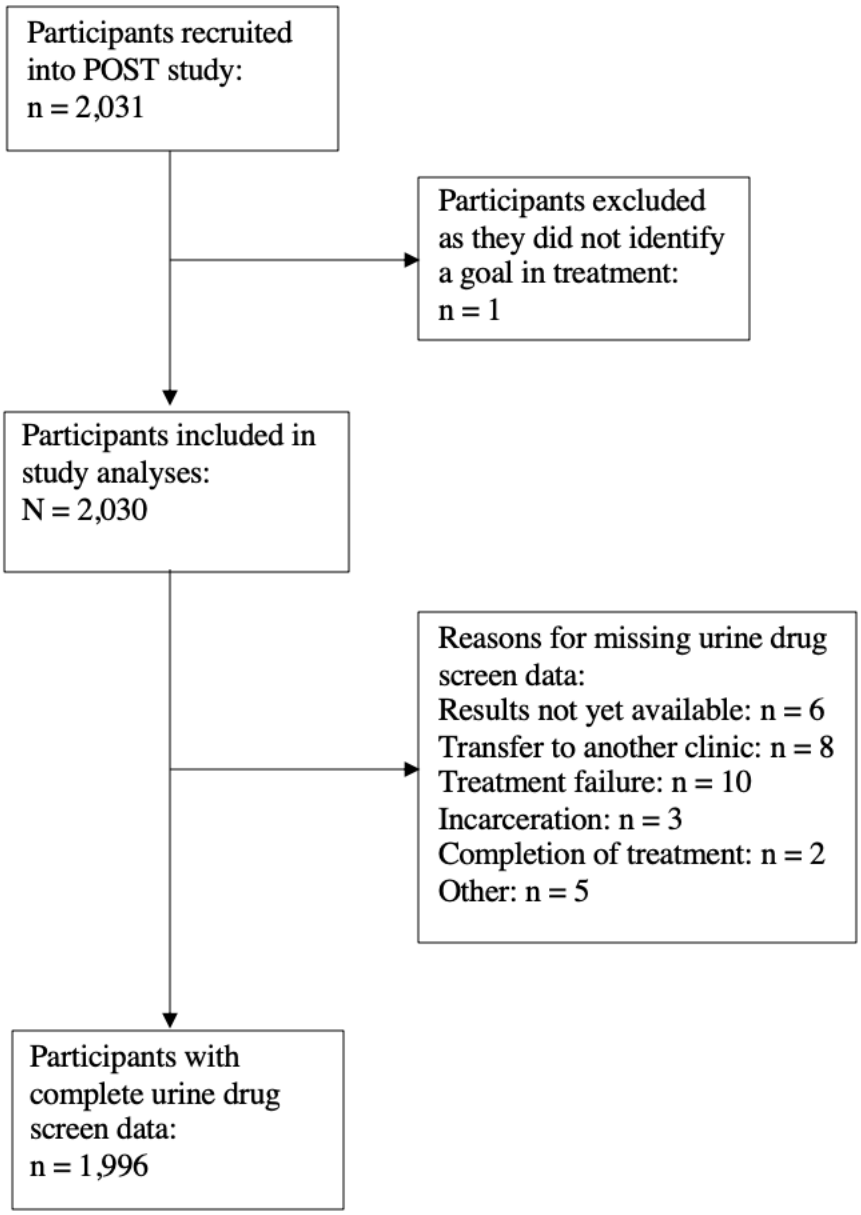
[a] Model is adjusted for age, sex, type of treatment (methadone or buprenorphine-naloxone), dose, length of time in treatment, and opioid abstinence at baseline.

[b] Participants with missing data in any of the included covariates are excluded due to complete case analysis (missing urine drug screen data: n = 36, missing sex: n = 1, missing length of time in treatment: n =1).

[c] Excluding 14 outliers detected using deviance residuals less than -2 from the analysis

Figure 1 Legend:
Study Flow Diagram. POST = Pharmacogenetics of Opioid Substitution Treatment Response

**Figure 1**. Study flow diagram.



**Supplementary Table 1 for Peer-Review**. Multivariable model of the association between patient goals and abstinence from opioid use for 3 months following study entry including all covariates.

| | *Complete case analysis*[a] **(n = 1, 994**[b]**)** | | | *Sensitivity analysis excluding outliers* **(n = 1,980)**[a,c] | | |
|---|---|---|---|---|---|---|
| **Covariate** | **OR** | **95% CI** | ***p*** | **OR** | **95% CI** | ***p*** |
| Control cravings/withdrawal | 0.76 | 0.56, 1.03 | 0.078 | 0.73 | 0.54, 0.99 | 0.044 |
| Maintain or stabilize medication dose | 1.15 | 0.74, 1.79 | 0.523 | 1.24 | 0.79, 1.95 | 0.354 |
| "Live a normal life" | 1.02 | 0.77, 1.35 | 0.879 | 0.98 | 0.74, 1.31 | 0.902 |
| Manage pain | 1.0 | 0.73, 1.36 | 0.976 | 0.96 | 0.70, 1.32 | 0.806 |
| "Stay or get clean" | 0.73 | 0.59, 0.91 | 0.005 | 0.70 | 0.56, 0.87 | 0.001 |
| Stop or taper off treatment | 1.0 | 0.80, 1.27 | 0.974 | 1.01 | 0.80, 1.27 | 0.954 |
| Age in years | 1.0 | 0.99, 1.01 | 0.730 | 1.0 | 0.99, 1.01 | 0.715 |
| Female sex | 1.13 | 0.93, 1.37 | 0.223 | 1.14 | 0.94, 1.39 | 0.194 |
| Type of treatment<br>Methadone<br>Buprenorphine-naloxone | <br>[ref]<br>1.88 | <br><br>1.40, 2.50 | <br><br>< 0001 | <br>[ref]<br>2.13 | <br><br>1.58, 2.86 | <br><br>< 0.001 |
| Medication dose (mg/day) | 1.0 | 0.99, 1.01 | 0.057 | 1.0 | 1.0. 1.0 | 0.015 |
| Years in treatment | 1.03 | 1.01, 1.04 | 0.013 | 1.03 | 1.01, 1.05 | 0.006 |
| Opioid abstinence at baseline | 5.34 | 4.23, 6.74 | <0.001 | 6.15 | 4.83, 7.84 | < 0.001 |

OR = Odds Ratio, CI = Confidence Interval

Variance inflation factor = 1.19

Hosmer-Lemeshow $\chi^2$ 5.93, $p = 0.656$

[a] Model is adjusted for age, sex, type of treatment (methadone or buprenorphine-naloxone), dose, length of time in treatment, and opioid abstinence at baseline.

[b] Participants with missing data in any of the included covariates are excluded due to complete case analysis (missing urine drug screen data: n = 36, missing sex: n = 1, missing length of time in treatment: n =1).

[c] Excluding 14 outliers detected using deviance residuals less than -2 from the analysis

**Supplementary Table 2 for Peer-Review**. Multivariable model of the association between number of self-reported goals and abstinence from opioid use for 3 months following study entry.

| | (n = 1, 994[b]) | | |
|---|---|---|---|
| **Covariate** | **OR** | **95% CI** | ***p*** |
| Number of goals reported | | | |
| One | [ref] | | |
| Two | 0.93 | 0.75, 1.15 | 0.497 |
| Three or more | 0.70 | 0.49, 1.0 | 0.049 |
| Age in years | 1.0 | 0.99, 1.01 | 0.600 |
| Female sex | 1.14 | 0.94, 1.38 | 0.197 |
| Type of treatment | | | |
| Methadone | [ref] | | |
| Buprenorphine-naloxone | 1.88 | 1.41, 2.52 | < 0.001 |
| Medication dose (mg/day) | 1.0 | 0.99, 1.01 | 0.055 |
| Years in treatment | 1.03 | 1.01, 1.05 | 0.004 |
| Opioid abstinence at baseline | 5.41 | 4.30, 6.82 | <0.001 |
| OR = Odds Ratio, CI = Confidence Interval | | | |

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation | Included on page: |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Abstract |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Abstract |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 (intro, paragraphs 1-3) |
| Objectives | 3 | State specific objectives, including any pre-specified hypotheses | 3 (intro, paragraph 5) |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 3-4 (Methods, Data section) |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 3-4 (Methods, Data section) |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 3 (Methods, paragraph 1, 3) |
| | | *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls | |
| | | *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed | |
| | | *Case-control study*—For matched studies, give matching criteria and the number of controls per case | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4 (Statistical analysis, paragraph 2) |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 4 (Methods) |

| | | | |
|---|---|---|---|
| Bias | 9 | Describe any efforts to address potential sources of bias | Methods (Data), Limitations (page 7) |
| Study size | 10 | Explain how the study size was arrived at | Figure 1 Study Flow Diagram |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Methods, Statistical analysis page 4 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Methods, Statistical analysis page 4 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | |
| | | (*c*) Explain how missing data were addressed | Page 5 first paragraph |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed | |
| | | *Case-control study*—If applicable, explain how matching of cases and controls was addressed | |
| | | *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | |
| Continued on next page | | | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Study flow diagram Figure 1 |
| | | (b) Give reasons for non-participation at each stage | Study flow diagram Figure 1 |
| | | (c) Consider use of a flow diagram | Study flow diagram Figure 1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Table 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Table 1 |

| | | | |
|---|---|---|---|
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | Table 1 |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | Table 1 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Table 2 |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Results page 5, paragraph 3 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Discussion page 6 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Discussion page 7 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Discussion page 6 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Discussion page 7 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Title page |

Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | | |
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| Objectives | 3 | State specific objectives, including any prespecified hypotheses |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| Bias | 9 | Describe any efforts to address potential sources of bias |
| Study size | 10 | Explain how the study size was arrived at |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding |
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| | | (*c*) Explain how missing data were addressed |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy |
| | | (*e*) Describe any sensitivity analyses |

Continued on next page

**Results**

| | | | | | |
|---|---|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | | | |
| | | (b) Give reasons for non-participation at each stage | | | |
| | | (c) Consider use of a flow diagram | | | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | | | |
| | | (b) Indicate number of participants with missing data for each variable of interest | | | |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | | | |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | | | |
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| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | | | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | | | |
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| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | | | |
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| Key results | 18 | Summarise key results with reference to study objectives | | | |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | | | |
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| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | | | |
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BMJ Open

# Are patients' goals in treatment associated with expected treatment outcomes? Findings from a mixed-methods study on outpatient pharmacological treatment for opioid use disorder.

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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-044017.R2 |
| Article Type: | Original research |
| Date Submitted by the Author: | 11-Dec-2020 |
| Complete List of Authors: | Rosic, Tea; McMaster University, Department of Psychiatry and Behavioral Neurosciences; McMaster University, Department of Health Research, Evidence and Impact<br>Naji, Leen; McMaster University, Department of Family Medicine, McMaster University, Hamilton, Ontario, Canada<br>Panesar, Balpreet; McMaster University, Neurosciences Graduate Program, McMaster University, Hamilton, Ontario, Canada<br>Chai, Darren; McMaster University, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada<br>Sanger, Nitika; McMaster University, Medical Science Gradaute Program<br>Dennis, Brittany; McMaster University, Department of Medicine, McMaster University, Hamilton, Ontario, Canada: 1280 Main St W, Hamilton, ON L8S 4L8<br>Marsh, David; Northern Ontario School of Medicine,<br>Rieb, Launette; University of British Columbia Faculty of Graduate Studies<br>Worster, Andrew; McMaster University, Division of Emergency Medicine<br>Thabane, Lehana ; McMaster University, Clinical Epidemiology & Biostatistics<br>Samaan, Zainab; McMaster University, Psychiatry and Behavioral Neurosciences |
| Primary Subject Heading: | Addiction |
| Secondary Subject Heading: | Patient-centred medicine, Addiction, Qualitative research |
| Keywords: | Adult psychiatry < PSYCHIATRY, Substance misuse < PSYCHIATRY, QUALITATIVE RESEARCH |
| | |

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# Are patients' goals in treatment associated with expected treatment outcomes? Findings from a mixed-methods study on outpatient pharmacological treatment for opioid use disorder.

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ABSTRACT

Objectives: Existing methods of measuring effectiveness of pharmacological treatment for opioid use disorder (OUD) are highly variable. Therefore, understanding patients' treatment goals is an integral part of patient-centered care. Our objective is to explore whether patients' treatment goals align with a frequently used clinical outcome, opioid abstinence.

Design: Triangulation mixed-methods design

Setting and Participants: We collected prospective data from 2,030 participants who were receiving methadone or buprenorphine-naloxone treatment for a diagnosis of OUD in order to meet study inclusion criteria. Participants were recruited from 45 centrally-managed outpatient opioid agonist therapy clinics in Ontario, Canada. At study entry, we asked, "What are your goals in treatment?" and used Nvivo software to identify common themes.

Primary outcome measure: Urine drug screens (UDS) were collected for 3 months post-study enrolment in order to identify abstinence versus ongoing opioid use (mean number of UDS over 3 months = 12.6, standard deviation (SD) = 5.3)). We used logistic regression to examine the association between treatment goals and opioid abstinence.

Results: Participants had a mean age of 39.2 years (SD = 10.7), 44% were female, and median duration in treatment was 2.6 years (interquartile range 5.2). Six overarching goals were identified from patient responses, including "stop or taper off of treatment" (68%), "stay or get clean" (37%), and "live a normal life" (14%). Participants reporting the goal "stay or get clean" had lower odds of abstinence at 3 months than those who did not report this goal (OR = 0.73, 95% CI 0.59-0.91, $p$ = 0.005). Although the majority of patients wanted to taper off or stop medication, this goal was not associated with opioid abstinence, nor were any of their other goals.

Conclusions: Patient goals in OUD treatment do not appear to be associated with program measures of outcome (i.e., abstinence from opioids). Future studies are needed to examine outcomes related to patient-reported treatment goals found in our study; pain management, employment, and stopping/tapering treatment should all be explored.

Strengths and limitations of this study:

- This study is strengthened by its large sample size (2,000 participants) and multisite design.
- Participating clinics follow a harm-reduction approach to treatment and these findings may not generalize to abstinence-based treatment settings.
- The goals and treatment outcomes of patients newly entering treatment may differ from those of patients who have been in treatment longer and may not be captured in this study.

Key words: opioid agonist treatment, patient-centred care, methadone, buprenorphine, treatment goals

## INTRODUCTION

Opioid use disorder (OUD) remains a clinical and public health challenge, with ongoing high rates of opioid use and overdose deaths.[1] Consequently, growing numbers of patients are enrolled in pharmacological treatment for OUD.[2,3] Methadone, a full opioid agonist, and buprenorphine, a partial opioid agonist, are the two most commonly used medications in the management of OUD; they act to reduce cravings and withdrawal, and support abstinence from ongoing opioid use.[4] Evidence from systematic reviews of experimental studies indicates that both medications reduce opioid use.[5,6] However, not all patients have favorable outcomes,[7,8] and patients who continue to use opioids during treatment have a high risk of overdose and death.[9,10] Other treatments, including heroin-assisted treatment, are available in some jurisdictions for patients who have limited response to treatment with first-line medications.[11]

Better understanding patients' goals in treatment is considered increasingly important within the field of substance use and addiction.[12-14] The now well-known concept of *patient-centered care* was originally coined with the definition of "care that is respectful of, and responsive to, individual patient preferences, needs, and values",[15,16] and is demonstrated to have a significant impact on patients' outcomes and satisfaction in treatment.[17] Increasing attention is being paid to patients' goals and the implementation of patient-centred care principles in addiction treatment.[18]

Identifying core treatment outcomes is an active area of investigation within the field of Addiction Medicine.[19] Unfortunately, there is still significant variability in the outcomes used to evaluate the effectiveness of pharmacological treatment for OUD.[20, 21] How to best measure and assess treatment outcomes remains uncertain, and current practices risk being based upon convenience. Opioid use, measured by urine drug screens (UDS), and retention in treatment are the most commonly used primary outcomes measured in clinical studies and treatment programs;[21] however, it is unknown how well these outcomes are associated with patients' goals in treatment. Personal and social functioning outcomes are, in contrast, much less commonly assessed.[21] As core endpoints and outcome sets for studies of OUD are developed, it is critical to understand which goals in treatment are important to patients and how to best measure them.

In a recent study by Sanger et al., 2020, we used qualitative analysis methods to examine patient-reported treatment goals in a cohort of more than 2,000 patients receiving outpatient pharmacological treatment for OUD.[22] We identified six distinct goals in treatment from patient responses, including to control cravings or withdrawal, to maintain or stabilize medication dose, to stop or taper off treatment, to "stay or get clean", to manage pain, and to "live a normal life".[22]

The objective of the present study was to explore whether these patient-reported treatment goals are associated with abstinence from opioid use (a frequently measured program outcome). We hypothesized that patient goals related to drug use would be associated with opioid use during treatment; meanwhile, goals unrelated to drug use would have no association with UDS results.

## METHODS

### *Data*

We collected prospective observational data from 2,030 participants recruited from 45 outpatient clinics in the Pharmacogenetics of Opioid Substitution Treatment Response (POST) study. To meet study inclusion criteria, participants were required to be at least 16 years of age and receiving pharmacological treatment with methadone or buprenorphine-naloxone (for any length of time) for a diagnosis of OUD, as per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).[23] The diagnosis of OUD was made by treating

physicians according to DSM-5 criteria and is an eligibility criterion for treatment entry and clinical follow up at the outpatient clinics included in this study. No other inclusion or exclusion criteria were applied in order to increase the generalizability of this study. Participants completed face-to-face interviews at study entry to collect information on demographic and clinical characteristics.

We used a triangulation mixed-methods design to combine quantitative and qualitative data collection, where both quantitative and qualitative data were collected within one study instrument using closed- and open-ended questions.[24,25] At study intake, participants were interviewed by trained research staff to obtain information on sociodemographic and clinical information, medical history, and substance use history. Research staff had a background in addiction research, as they previously participated in recruitment of participants for a study investigating genetic influences on methadone treatment.[26] Their experience allowed for familiarity of addiction-related terms used in interview responses; however, research staff were not known to the participants of this study. Study interviews were conducted in-person at the CATC. The interview data used in this study is from participants recruited from May 2018 until August 2019. During the interview, all participants who met the inclusion and exclusion criteria above were asked the open-ended question, "What are your goals in treatment". Details regarding the study settings and data collection are outlined in a previous study looking at OUD-related patient important outcomes.[22] Verbal responses, in their entirety, were transcribed by research staff word-for-word in online anonymized records, where each participant was given an anonymized record number.

We collected the results of UDSs for opioids for each participant for three months following study entry to assess treatment outcome. The FaStep Assay (Trimedic Supply Network Ltd, Concord, Ontario, Canada) was used to detect morphine, oxycodone, fentanyl, methadone metabolite, and buprenorphine, as well as other non-opioid substances.[27] Though other methods may be used to assess ongoing opioid use during treatment, such as saliva and hair tests, as well as self-report,[28] UDSs are collected as part of routine clinical protocol in the clinics participating in this study and are a recommended method of assessment based on Canadian Guidelines.[4] UDSs were collected following clinic protocol (typically weekly or biweekly). For each participant, we calculated the percentage of opioid-positive UDSs by dividing the number of opioid-positive urines by the number of urine samples taken. Abstinence from opioids

was selected as our primary study outcome as it is a routinely measured treatment outcome in both clinical practice and research studies.

Another commonly studied treatment outcome, retention in treatment, was not formally assessed in the present study for two reasons. First, treatment retention is not equivalent to the duration of time enrolled in this study (as our study used a naturalistic design and enrolled patients in various stages of their treatment). Second, with the exception of patients who have entered treatment for the first time, there exists some uncertainty in defining treatment retention because patients frequently enter and discontinue treatment at various points in their course of illness. Instead, we asked participants to report their length of time enrolled in this treatment episode (as a proxy for treatment retention) and adjusted all study analyses for length of time in treatment.

This study was reviewed and approved by the Hamilton Integrated Research Ethics Board (project ID 4556) and conducted in accordance with its ethical guidelines. We report methods and quantitative results in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[29]

*Qualitative analysis*

The qualitative approach used to analyze the data was data-driven thematic analysis.[30] We began by familiarizing ourselves with the data through active, repeated reading of the interview responses and began to recognize emerging patterns. This phase of data familiarization also allowed us to minimize typographical errors present in the free text responses. We began phase two by generating initial codes using NVivo software QSR International [Americas] Inc., Burlington, Massachusetts, USA) for qualitative analysis to identify common themes from patient answers.[31] We began cataloguing main ideas, phrases, and patterns into meaningful nodes using word and text queries, and a review of the transcribed data. Word and text queries helped us capture the patterns in data and improve analytic accuracy by identifying stemmed variants. Each data item was given equal attention and in addition to text and word queries, key phrases were tagged within each data item. This phase is characterized by the generation of a codebook that provided specific definitions of the key phrases, words and patterns. The next phase consisted of the labelling of some nodes as themes and the

collapsing of related nodes into one node, eventually being labelled as a themes or sub-themes. The final phase consisted of a review of identified themes and resultant reworking of themes to better establish coherent patterns within each theme. Defining and refining of each theme followed this phase, where patterns and content were considered before choosing relevant and reflective theme names.[30,32] To increase rigour in our analysis we used investigator triangulation, where phases concerning the generation of themes involved the consultation of four investigators to ensure incorporation of diverse perspectives. This was reflected in the iterative review of nodes and patterns, where meaningfulness of coding was discussed and was reassessed at every identified phase. We report qualitative methods and results in accordance with the Standards of Reporting Qualitative Research (SRQR).[33]

*Quantitative analysis*

We conducted all quantitative analyses using Stata Version 15.1 (StataCorp LP, College Station, TX, USA). We report demographic and clinical data using mean and standard deviation (SD) for normally distributed continuous variables and median with quartiles 1 and 3 or interquartile range (IQR) for skewed data. We report categorical variables as frequency with percentage. We summarize the results of UDSs in three ways: 1) the mean number of UDSs collected; 2) the percentage of opioid-positive UDSs; and 3) abstinence from opioid use, defined as no opioid-positive UDSs during the 3-month time period.

We used logistic regression analysis to examine the association between patient goals in treatment and abstinence from opioid use, adjusting for other important covariates. We constructed a logistic regression model, using the dependent variable abstinence from opioid use throughout the 3 months following study entry. We included the six identified treatment goals in the model and controlled for other factors believed to impact ongoing opioid use in treatment, including age, sex,[34,35] type of treatment (methadone or buprenorphine-naloxone), medication dose,[36] length of time in treatment,[37] and abstinence from opioids at baseline. We also conducted an additional logistic regression to determine whether the number of goals reported by participants was associated with opioid abstinence, as patients who report more treatment needs tend to have more opioid use.[38] Results are reported as odds ratios (OR) with 95% confidence intervals (CI) and associated *p* values. We report the estimates of effect for our main variables of interest (treatment goals)

in the results table and describe all variables adjusted for in a footnote in the table in order to focus solely on the variables of interest to our specific study question. We assessed for multicollinearity using variance inflation factor and examined model diagnostics using the Hosmer-Lemeshow statistic and deviance residuals. We conducted a sensitivity analysis after excluding observations with a deviance residual lower than -2 or higher than 2. Our sample size of 2,030 participants and event rate of more than 1,000 participants abstinent from opioids is adequate, based on the rule of thumb for number of events needed (n = 10) per covariate included in logistic regression analysis.[39]

Missing data were identified and reported for each variable of interest. There were less than 5 cases with missing data for baseline demographic or clinical variables. For 3-month UDS, missing data affected 34 participants (1.7%). Reasons for missing 3-month UDS data included: results not yet available (n = 6), transfer to another clinic (n = 8), treatment failure (n = 10), incarceration (n = 3), completion of treatment (n=2), and other (n = 4), such as hospitalization, moving, or never starting treatment. Due to the low percentage of missing data, all missing data were handled by available case analysis.

**Patient and Public Involvement**

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

*Participant characteristics and goals in treatment*

Altogether, 2,030 participants were included in the analyses (Figure 1; Study flow diagram), with a mean age of 39.2 years (SD = 10.7) and 44% were female (Table 1). The majority of participants were receiving treatment with methadone (78.9%) compared to buprenorphine-naloxone (21.1%) and the median length of time in treatment was 2.6 years (IQR 5.2). UDSs collected for the three months of study duration were available for 1,996 participants. Among these participants, 57% were abstinent from opioid use during those 3 months. Ultimately, we identified six distinct “themes” or “goals” in treatment: 1) to control cravings or withdrawal, 2) to maintain or stabilize medication dose, 3) to stop or taper off treatment, 4) to “stay or get clean”, 5) to manage pain, and 6) to “live a normal life”, as

presented by our previous paper looking at patient important outcomes in the OUD population receiving MAT.[22] The "control cravings or withdrawal" theme consisted of participants responses stating they would like to avoid withdrawal or control their cravings. Participant responses grouped in the second theme of "no changes in treatment" were made up of responses indicating that they wanted to maintain OSAT doses, stabilize their OSAT dose, or did not have any reported goals. The third goal to "stop OSAT treatment" had goals to stop treatment completely, to not be dependent on OSAT, to taper off, or reduce dose. Participant goals such as wanting to get clean, stay clean, achieve abstinence, or achieve sobriety from all drugs were included in the fourth goal of "avoiding illicit drugs". The fifth theme of "pain management" either mentioned chronic pain, or pain management in general. The sixth theme of "living a normal life" consisted of responses such as wanting a stable life, normal life, to get qualifications related to education, job or work, to achieve good mental health, or wanting to support their family.[22]

The most common patient-reported goal was to "stop or taper off treatment" (68%; see Table 1 for all goals). Other goals included to "stay or get clean" (37%), to "live a normal life" (14%), and to "control cravings or withdrawal" (12%). Most participants (60.2%) reported one treatment goal (mean number of goals = 1.49, SD = 0.67). We reported demographic and clinical characteristics associated with different treatment goals in a previously published paper.[22]
The proportion of participants treated with methadone (as compared to buprenorphine-naloxone) was 79% for the goal "stop or taper off treatment", 78% for "stay or get clean", 84% for "live a normal life", 86% for "manage pain", 81% for "control cravings or withdrawal", and 75% for "maintain or stabilize medication dose". The median length of time in treatment at the time of study recruitment was 3 years (IQR = 5) for the goal "stop or taper off treatment", 2 years (IQR = 4.5) for "stay or get clean", 3 years (IQR = 6.2) for "live a normal life", 4 years (IQR = 8) for "manage pain", 2 years (IQR = 5.4) for "control cravings or withdrawal", and 5 years (IQR = 8) for "maintain or stabilize medication dose". Abstinence from opioid use at study entry was observed in 33% of participants reporting the goal to "stop or taper off treatment", 28% for "stay or get clean", 31% for "live a normal life", 30% for "manage pain", 31% for "control cravings or withdrawal", and 45% for "maintain or stabilize medication dose".

*Association between patients' goals in treatment and 3-month abstinence from opioid use (MAT program goal)*

We examined the association between patient goals and abstinence from opioid use for 3 months following study entry, adjusting for other characteristics previously shown to be associated with ongoing opioid use (Table 2). Paradoxically, participants

reporting the goal "to stay or get clean" had 27% lower odds of abstinence from opioids at 3 months (OR = 0.73, 95% CI 0.59-0.91, $p$ = 0.005), even after adjusting for baseline abstinence from opioid use. No other patient-reported goals in treatment were significantly associated with 3-month abstinence.

Good model fit was assessed using the Hosmer-Lemeshow statistic ($\chi 2$ = 5.93, p = 0.656) and multicollinearity was not a concern (mean VIF 1.19). Using deviance residuals, we detected 14 outliers with deviance residuals greater than an absolute value of 2. We conducted a post-hoc sensitivity analysis removing outliers and found that participants who reported the goal "to control cravings or withdrawal" also had significantly lower odds of opioid abstinence at 3 months (OR = 0.73, 95% CI 0.54-0.99, $p$ = 0.044; Supplementary Table 1). There were no other significant changes to the results upon removing outliers.

Finally, we examined the association between number of reported goals and abstinence from opioid use for 3 months (Supplementary Table 2). As compared to reporting one goal in treatment, reporting two goals was not associated with opioid use (OR = 0.93, 95% CI = 0.75, 1.15, $p$ = 0.497), however reporting three or more goals may be associated with lower odds of abstinence from opioids (OR = 0.70, 95% CI = 0.49, 1.0, $p$ = 0.049).

## DISCUSSION

In this mixed-methods study, we examined treatment goals reported by more than 2,000 patients receiving pharmacological treatment for OUD to determine their association with the frequently measured treatment outcome, opioid use. Participants reporting the goals to "stay or get clean" and to control cravings or withdrawal were less likely to be abstinent from opioids during the next 3 months of treatment than participants who did not report those goals. Other goals related to termination of treatment, pain, or personal or social functioning were not associated with opioid use. These findings suggest that abstinence from opioids, a commonly used treatment outcome measured in clinical trials, does not reflect what patients want out of treatment, and raises questions about the alignment between treatment outcomes and patient goals.[40]

We found that patients who identified goals related to stopping drug use or controlling OUD symptoms had worse outcomes in treatment as measured by UDS. There is a rich literature examining the apparent contradiction between abstinence-related goals and subsequent drug-taking behaviors. This is in essence

the focus of motivational interviewing[41] in which clinicians help patients develop motivation through recognizing discrepancies between their current situation and their goals, shifting the balance towards change.[42] One possible explanation is that patients who were experiencing worse outcomes in treatment or higher severity of illness were more likely to report goals regarding management of substance use symptoms and abstinence from drug use, thus also increasing the likelihood that they experienced ongoing opioid use. Another possibility is that participants who had achieved abstinence or had improvements in OUD withdrawal symptoms may have been less likely to identify the same goals. Nonetheless, exploring why patients wishing to abstain from opioid use are not achieving this goal is an area requiring further study. Beyond quantitatively examining factors associated with ongoing substance use, previous qualitative studies that explore patient perceptions of barriers and facilitators to achieving abstinence are illuminating and may inform future interventions and research.[43-45]

Although the majority of patients wanted to taper off or stop treatment, this goal had no association with abstinence from opioid use. One possible explanation is that participants may have been unhappy with treatment and therefore non-adherent. Factors associated with non-adherence to opioid agonist treatments have been previously studied.[46-49] There is a vast literature on factors affecting patient adherence to treatment in general and, notably, no single explanation sufficiently accounts for variation in adherence.[50] Authors in this field have suggested considering the patient's experience of illness and its meaning as important factors to study in understanding adherence to treatment.[50, 51] This finding calls into question the rationale for entering and continuing pharmacological treatment while continuing to use opioids for this group of patients. Furthermore, this is a particularly important finding, given that retention in treatment is amongst the most consistently measured outcomes,[19] and guidance around taper and discontinuation of long-term opioid agonist treatments for opioid use disorder is limited.[4,52] Studies examining opioid agonist tapers have identified challenges and risks of poor outcomes[53,54] including withdrawal symptoms, return to drug use, pain, psychiatric symptoms, hospitalization, and death.[55,56] A previous study found that patients' interest in stopping treatment was associated with shorter duration of treatment and lack of concern about relapse to opioid use.[57] This is concerning as one would hope patients planning to stop treatment would be reliably abstinent from opioids. What distinguishes this group of patients who wish to discontinue treatment? Whether some of

these patients are mandated to be in treatment is unknown. Better understanding patients' reasons for wanting to stop or taper treatment and examining outcomes for patients who initiate an opioid agonist taper is imperative.

Other patient identified goals in treatment that were not associated with the results of their UDS, included goals around pain management, and the goal "to live a normal life". This suggests that clinicians and researchers may require additional tools to measure outcomes related to those patient-important treatment goals. Tools validated to assess pain in this population include the Brief Pain Inventory[58,59] and social functioning may be examined using the Maudsley Addiction Profile.[60] A more nuanced understanding of specific goals around personal and social functioning, on a population and individual level, is required in order to be able to appropriately assess and address these goals during treatment. Overall, our finding that results of UDSs are not associated with all patient goals in treatment is expected as UDSs results would not be expected to be a proxy for all of the different goals. However, this study adds evidence to the notion that traditional metrics of success in opioid use disorder treatment are insufficient in isolation. It is important to note that although patient goals appear to have limited predictive value on opioid use during treatment, this does not imply that clinicians should not ask patients about their treatment goals. It is not uncommon that patients have goals that are not achieved in treatment (e.g., weight loss, increased physical activity) and this does not mean that clinicians or patients should give up on these goals or should not enquire about them. Rather, we must consider how well traditional metrics of treatment success align with desired treatment outcomes for all stakeholders, especially patients, and consider additional ways to evaluate and improve treatment success based on patients' self-reported goals.

Finally, in a previous paper, we examined group differences between participants selecting each treatment goal.[22] Females were more likely to report the goal of stopping treatment. Older age, first exposure to opioids through physician prescription, and unemployment were all associated with greater odds of reporting goals related to pain management.[22] These findings indicated that, unsurprisingly, patients' characteristics are associated with their treatment goals and may help to guide focused questioning and evaluation of patients' goals in treatment.

This study has a number of potential limitations. First, this study interprets and summarizes the patients' narrative when expressing their goals in treatment using qualitative methods; however, this interpretation carries limitations related to the potential influence of social desirability bias and the influence of contextual factors on patients' responses that have not been explored in this study. Though beyond the scope of this paper, sociological approaches to qualitative analysis include critical appraisal of the circumstances of the participant and the context in which statements are expressed. Furthermore, there may be a healthy user/volunteer bias,[61] such that individuals with better outcomes in treatment may have been more likely to participate. Additionally, the goals and treatment outcomes of patients newly entering treatment may differ from those of patients who have been in treatment longer. Patients who may have successfully achieved their goal of treatment termination were not captured by this study since they would no longer be on OUD thus not recruited. The findings in this study may not generalize to settings in which opioid agonist medications take on a primarily abstinence-based role in treatment. In Canada, pharmacological treatment for OUD is provided largely in a harm-reduction model, in which retention in treatment is not contingent on abstinence from opioids or non-opioid substances. This study did not measure patient's satisfaction or perception of treatment success or perception of meeting their goals. Future studies that examine patient satisfaction in treatment may wish to determine whether perception of treatment success correlates with program-measured outcomes such as opioid abstinence.

## CONCLUSION

Patients report a number of different goals in their treatment for OUD, which are not associated with traditional goals of treatment programs and outcomes measured in clinical settings (abstinence from opioid use measured by UDS). We found that patients who identified goals related to stopping drug use or controlling OUD symptoms were more likely to have ongoing opioid use. However, goals unrelated to drug use carried no significant association with opioid use status. Patients reporting the goal of wanting to stop treatment were no more likely to be abstinent from opioids. The patient-identified goals to manage pain or "live a normal life" had no association with ongoing opioid use. Future studies are needed to examine outcomes related to the goals in treatment identified in our study. Are these goals being met in treatment? For example, do patients feel their pain is well managed? Do they achieve employment? Can they achieve

the goal of stopping treatment without adverse consequences? As core outcome sets are developed, patient-important outcomes remain essential to consider and may help with implementing patient-centered approaches to treatment.

ACKNOWLEDGMENTS

We would like to thank the Pharmacogenetics of Opioid Substitution Treatment Response (POST) study participants for their time and contributions, without which this study would not be possible.

**Authors' contributions**

TR, LN, BP, NS, BBD, and ZS are responsible for the study concept and design. TR, BP, LT and ZS developed the methods and data analysis. TR conducted quantitative analysis and BP conducted qualitative analysis. TR wrote the first draft of the manuscript, and TR, LN, BP, DBC, NS, BBD, DCM, LR, AW, LT, and ZS, contributed to writing and critically revising the final manuscript. All authors reviewed and approved the final manuscript.

**Data availability**

Data are available upon reasonable request

**Role of funding source**

This study was supported by research grants from the Canadian Institutes for Health Research (grant numbers PJT-156306 and SHI-155404). The funding bodies had no role in the design, analysis, interpretation, or publication of results.

**Declaration of interests**

Dr. Marsh reports Salary income as Chief Medical Director, Canadian Addiction Treatment Centres and as Associate Dean Research, Innovation and International Relations, Northern Ontario School of Medicine. The other study authors declare no conflicts of interest.

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**Table 1.** Characteristics of participants at study entry (N = 2,030).

| Characteristic | Statistic |
|---|---|
| **Demographic and clinical** | |
| Age in years; mean (SD) | 39.2 (10.7) |
| Female sex [a]; *n* (%) | 894 (44.1) |
| Type of treatment; *n* (%) | |
| Methadone | 1601 (78.9) |
| Buprenorphine-naloxone | 429 (21.1) |
| Dose in mg/day; mean (SD) | |
| Methadone | 70.5 (41.4) |
| Buprenorphine-naloxone | 12.0 (6.7) |
| Years in treatment [a]; median (IQR) | 2.6 (5.2) |
| Abstinence from opioid use at baseline [b]; *n* (%) | 646 (31.9) |
| Number of opioid urine drug screens at 3 months [c]; mean (SD) | 12.6 (5.3) |
| Median percentage of opioid-positive urine drug screens at 3 months [c]; median (Q1, Q3) | 0 (0, 20) |
| Abstinence from opioid use at 3 months [c]; *n* (%) | 1,127 (56.5) |
| **Patient-reported goals in treatment [d]** | |
| Number of goals reported; *n* (%) | |
| One | 1222 (60.2%) |
| Two | 643 (31.7%) |
| Three | 150 (7.4%) |
| Four | 13 (0.64%) |
| Five | 2 (0.1%) |
| Control cravings/withdrawal | 247 (12.17%) |

| | |
|---|---|
| Maintain or stabilize medication dose | 122 (6.01%) |
| "Live a normal life" | 283 (13.94%) |
| Manage pain | 240 (11.82%) |
| "Stay or get clean" | 742 (36.55%) |
| Stop or taper off treatment | 1386 (68.28%) |

SD = Standard Deviation, Q1 = 25th percentile, Q3 = 75th percentile

[a] Data available for 2,029 participants.

[b] Data available for 2,028 participants.

[c] Data available for 1,996 participants (missing for 34 participants).

[d] Percentages sum to more than 100% as patients could report multiple goals in treatment.

**Table 2.** Multivariable model of the association between patient goals and abstinence from opioid use for 3 months following study entry.

| | ***Complete case analysis*** [a] **(n = 1, 994** [b]**)** | | | ***Sensitivity analysis excluding outliers*** **(n = 1,980)** [a,c] | | |
|---|---|---|---|---|---|---|
| **Covariate** | **OR** | **95% CI** | ***p*** | **OR** | **95% CI** | ***p*** |
| Control cravings/withdrawal | 0.76 | 0.56, 1.03 | 0.078 | 0.73 | 0.54, 0.99 | 0.044 |
| Maintain or stabilize medication dose | 1.15 | 0.74, 1.79 | 0.523 | 1.24 | 0.79, 1.95 | 0.354 |
| "Live a normal life" | 1.02 | 0.77, 1.35 | 0.879 | 0.98 | 0.74, 1.31 | 0.902 |
| Manage pain | 1.0 | 0.73, 1.36 | 0.976 | 0.96 | 0.70, 1.32 | 0.806 |
| "Stay or get clean" | 0.73 | 0.59, 0.91 | 0.005 | 0.70 | 0.56, 0.87 | 0.001 |
| Stop or taper off treatment | 1.0 | 0.80, 1.27 | 0.974 | 1.01 | 0.80, 1.27 | 0.954 |

OR = Odds Ratio, CI = Confidence Interval

Variance inflation factor = 1.19

Hosmer-Lemeshow $\chi^2$ 5.93, $p$ = 0.656

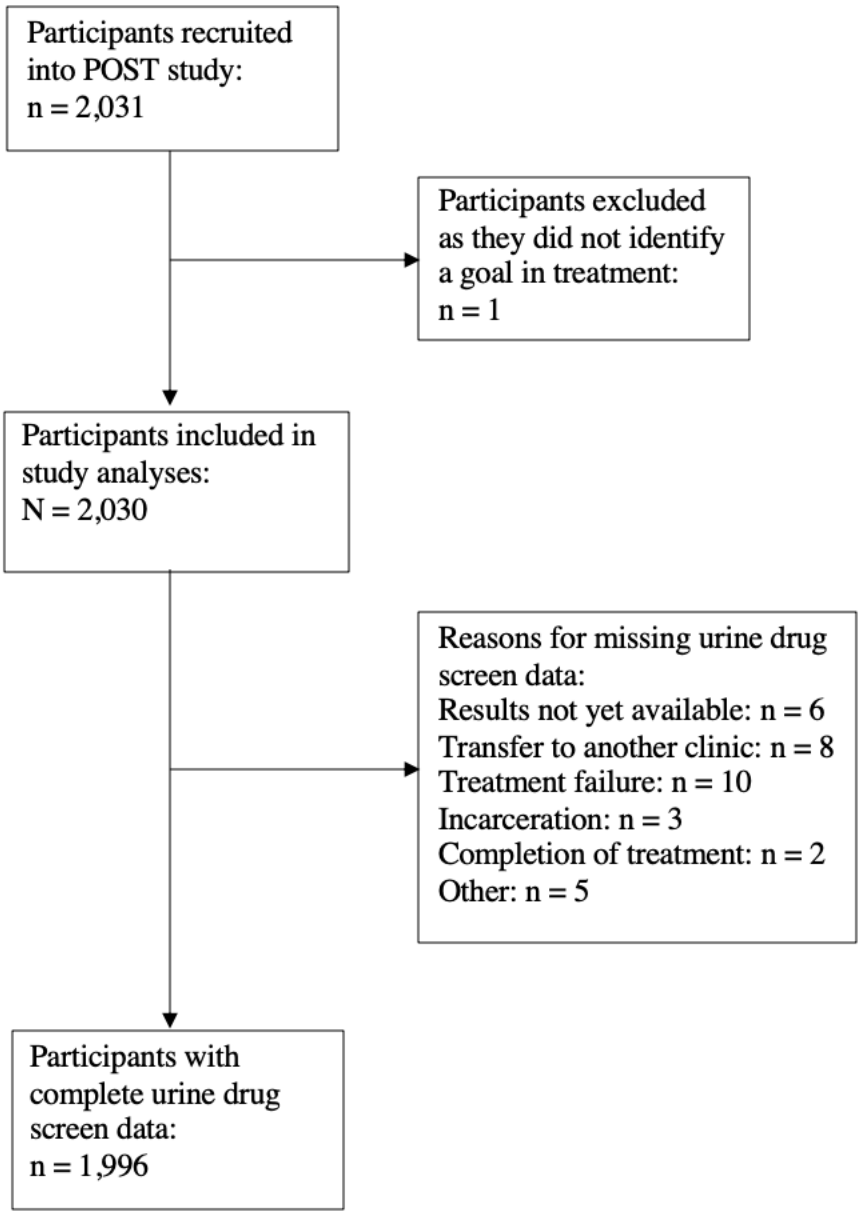
[a] Model is adjusted for age, sex, type of treatment (methadone or buprenorphine-naloxone), dose, length of time in treatment, and opioid abstinence at baseline.

[b] Participants with missing data in any of the included covariates are excluded due to complete case analysis (missing urine drug screen data: n = 36, missing sex: n = 1, missing length of time in treatment: n =1).

[c] Excluding 14 outliers detected using deviance residuals less than -2 from the analysis

Figure 1 Legend:
Study Flow Diagram. POST = Pharmacogenetics of Opioid Substitution Treatment Response

**Figure 1**. Study flow diagram.



**Supplementary Table 1 for Peer-Review**. Multivariable model of the association between patient goals and abstinence from opioid use for 3 months following study entry including all covariates.

| | *Complete case analysis*[a] **(n = 1, 994**[b]**)** | | | *Sensitivity analysis excluding outliers* **(n = 1,980)**[a,c] | | |
|---|---|---|---|---|---|---|
| **Covariate** | **OR** | **95% CI** | ***p*** | **OR** | **95% CI** | ***p*** |
| Control cravings/withdrawal | 0.76 | 0.56, 1.03 | 0.078 | 0.73 | 0.54, 0.99 | 0.044 |
| Maintain or stabilize medication dose | 1.15 | 0.74, 1.79 | 0.523 | 1.24 | 0.79, 1.95 | 0.354 |
| "Live a normal life" | 1.02 | 0.77, 1.35 | 0.879 | 0.98 | 0.74, 1.31 | 0.902 |
| Manage pain | 1.0 | 0.73, 1.36 | 0.976 | 0.96 | 0.70, 1.32 | 0.806 |
| "Stay or get clean" | 0.73 | 0.59, 0.91 | 0.005 | 0.70 | 0.56, 0.87 | 0.001 |
| Stop or taper off treatment | 1.0 | 0.80, 1.27 | 0.974 | 1.01 | 0.80, 1.27 | 0.954 |
| Age in years | 1.0 | 0.99, 1.01 | 0.730 | 1.0 | 0.99, 1.01 | 0.715 |
| Female sex | 1.13 | 0.93, 1.37 | 0.223 | 1.14 | 0.94, 1.39 | 0.194 |
| Type of treatment<br>Methadone<br>Buprenorphine-naloxone | <br>[ref]<br>1.88 | <br><br>1.40, 2.50 | <br><br>< 0001 | <br>[ref]<br>2.13 | <br><br>1.58, 2.86 | <br><br>< 0.001 |
| Medication dose (mg/day) | 1.0 | 0.99, 1.01 | 0.057 | 1.0 | 1.0. 1.0 | 0.015 |
| Years in treatment | 1.03 | 1.01, 1.04 | 0.013 | 1.03 | 1.01, 1.05 | 0.006 |
| Opioid abstinence at baseline | 5.34 | 4.23, 6.74 | <0.001 | 6.15 | 4.83, 7.84 | < 0.001 |

OR = Odds Ratio, CI = Confidence Interval

Variance inflation factor = 1.19

Hosmer-Lemeshow $\chi^2$ 5.93, $p = 0.656$

[a] Model is adjusted for age, sex, type of treatment (methadone or buprenorphine-naloxone), dose, length of time in treatment, and opioid abstinence at baseline.

[b] Participants with missing data in any of the included covariates are excluded due to complete case analysis (missing urine drug screen data: n = 36, missing sex: n = 1, missing length of time in treatment: n =1).

[c] Excluding 14 outliers detected using deviance residuals less than -2 from the analysis

**Supplementary Table 2 for Peer-Review**. Multivariable model of the association between number of self-reported goals and abstinence from opioid use for 3 months following study entry.

| | (n = 1, 994[b]) | | |
|---|---|---|---|
| **Covariate** | **OR** | **95% CI** | ***p*** |
| Number of goals reported | | | |
| One | [ref] | | |
| Two | 0.93 | 0.75, 1.15 | 0.497 |
| Three or more | 0.70 | 0.49, 1.0 | 0.049 |
| Age in years | 1.0 | 0.99, 1.01 | 0.600 |
| Female sex | 1.14 | 0.94, 1.38 | 0.197 |
| Type of treatment | | | |
| Methadone | [ref] | | |
| Buprenorphine-naloxone | 1.88 | 1.41, 2.52 | < 0.001 |
| Medication dose (mg/day) | 1.0 | 0.99, 1.01 | 0.055 |
| Years in treatment | 1.03 | 1.01, 1.05 | 0.004 |
| Opioid abstinence at baseline | 5.41 | 4.30, 6.82 | <0.001 |
| OR = Odds Ratio, CI = Confidence Interval | | | |

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation | Included on page: |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Abstract |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Abstract |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 (intro, paragraphs 1-3) |
| Objectives | 3 | State specific objectives, including any pre-specified hypotheses | 3 (intro, paragraph 5) |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 3-4 (Methods, Data section) |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 3-4 (Methods, Data section) |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 3 (Methods, paragraph 1, 3) |
| | | *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls | |
| | | *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed | |
| | | *Case-control study*—For matched studies, give matching criteria and the number of controls per case | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4 (Statistical analysis, paragraph 2) |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 4 (Methods) |

| | | | |
|---|---|---|---|
| Bias | 9 | Describe any efforts to address potential sources of bias | Methods (Data), Limitations (page 7) |
| Study size | 10 | Explain how the study size was arrived at | Figure 1 Study Flow Diagram |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Methods, Statistical analysis page 4 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Methods, Statistical analysis page 4 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | |
| | | (*c*) Explain how missing data were addressed | Page 5 first paragraph |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed | |
| | | *Case-control study*—If applicable, explain how matching of cases and controls was addressed | |
| | | *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | |
| Continued on next page | | | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Study flow diagram Figure 1 |
| | | (b) Give reasons for non-participation at each stage | Study flow diagram Figure 1 |
| | | (c) Consider use of a flow diagram | Study flow diagram Figure 1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Table 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Table 1 |

| | | | |
|---|---|---|---|
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | Table 1 |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | Table 1 |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Table 2 |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Results page 5, paragraph 3 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Discussion page 6 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Discussion page 7 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Discussion page 6 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Discussion page 7 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Title page |

Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| Bias | 9 | Describe any efforts to address potential sources of bias |
| Study size | 10 | Explain how the study size was arrived at |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding |
| | | (*b*) Describe any methods used to examine subgroups and interactions |
| | | (*c*) Explain how missing data were addressed |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy |
| | | (*e*) Describe any sensitivity analyses |

Continued on next page

**Results**

| | | | | | |
|---|---|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | | | |
| | | (b) Give reasons for non-participation at each stage | | | |
| | | (c) Consider use of a flow diagram | | | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | | | |
| | | (b) Indicate number of participants with missing data for each variable of interest | | | |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | | | |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | | | |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | | | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | | | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | | | |
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| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | | | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | | | |
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| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | | | |
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