PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	OPEN-LABEL DOSE-EXTENDING PLACEBOS FOR OPIOID USE DISORDER: A protocol for a randomized controlled clinical trial with methadone treatment
AUTHORS	Belcher, Annabelle; Cole, Thomas; Greenblatt, Aaron; Hoag, Stephen; Epstein, David; Wagner, Michael; Billing, Amy; Massey, Ebonie; Hamilton, Kristen; Kozak, Zofia; Welsh, Christopher; Weintraub, Eric; Wickwire, Emerson; Wish, Eric; Kaptchuk, Ted; Colloca, Luana

VERSION 1 - REVIEW

REVIEWER	Gabriel J Culbert, Assistant Professor University of Illinois at Chicago, College of Nursing, Chicago, IL, USA
REVIEW RETURNED	08-Dec-2018

GENERAL COMMENTS	Thank you for the opportunity to review manuscript ID bmjopen-2018-026604, entitled, Open-label dose-extending placebos for opioid use disorder: a protocol for a randomized controlled trial. This manuscript describes an ethical and well-designed study to assess the effectiveness of a dose-extending placebo as a novel and potentially effective adjunct treatment for OUD. The background, conceptualization, and description of procedures are excellent. Figure 1 is very helpful. The paper is very well organized and the writing is clear and concise. I have only minor comments. It may be important to briefly mention the clinical criteria (e.g. patient subjective mood, craving, substance use) that blinded clinicians will use to determine the need for dose escalation at week 3. This clinical decision determines the final maintenance dose (i.e. dependent variable). Evaluating these criteria through chart review at the trial's conclusion may be important for understanding which clinical criteria most influenced dose escalation - and possibly shed light on the underlying mechanism for placebo. If treatment providers are required to interact with research subjects or nursing staff in order to evaluate the need for dose escalation, it could lead to unblinding. Page 7; What is “Bayesian brain function”? Page 6; “raisk” should be “risk”. Page 7; “insert” should be “inert”

	Page 8; Line 52. The first part of this sentence states “the placebo intervention will enhance MMT outcomes…” I’m not sure this is consistent with what the authors have written previously. It may be more accurate to write, “…the placebo intervention will achieve equivalent MMT outcomes (decreased positive urine screens and increased treatment retention) at lower mean doses of methadone.

REVIEWER	Anita Srivastava Department of Family and Community Medicine, University of Toronto, Canada
REVIEW RETURNED	17-Jan-2019

GENERAL COMMENTS	This manuscript describes a randomized control trial looking at dose extending for methadone maintenance treatment. While this is an interesting premise, I have the following concerns about the study design: 1. Burden of disease: it would be helpful to know the average doses of methadone in their treatment program - are high doses really an issue? Moreover, there is some controversy over whether QT prolongation is dose dependent and, more importantly, if the clinical outcome (rather than the proxy measure of QT prolongation) of Torsades de Pointes is dose dependent. I think the authors should present some evidence on present day programs having high average methadone doses and on if keeping doses lower really does prevent Torsades. 2. I am concerned about the study design with respect to the use of placebo and blinding: in this case the participants will know which group they are assigned to and the subjective fear they have of their opioid dose not being high enough is not addressed - they will know that the dose extending pill that they are receiving is a placebo and this will still factor into their subjective withdrawal symptoms and requests for a higher dose. 3. Finally, it is hard to understand how their treating clinicians would not become aware of the participants' study assignment: surely the clinicians will hear from their patients about the dose extenders and so it cannot really be single-blind. Finally, clinicians will have a plethora of clinical experience in treating opioid use disorder patients with methadone and have some preconceptions of reasonable therapeutic dose ranges of methadone. If they are presented with a patient on a low dose of methadone with mild subjective withdrawal symptoms they may be more likely to increase the dose based purely on the low dose and previous clinical experience that most of their patients do well on higher doses. It seems that the only thing that could really get at the answer the authors are seeking is to keep participants blind to their methadone dose altogether and have dose increases made only by a preset protocol using a threshold score on a subjective withdrawal symptom scale. In summary, this is an interesting question -i.e. how much do subjective opioid withdrawal symptoms and fear of withdrawal play into potentially unnecessary and harmful dose increases - but I would like a stronger case to made that these dose increases are actually harmful and are a prevalent problem and I think the protocol needs to be adjusted so that participants are blind to their dose and dose adjustments are made based on the results of a subjective symptom scale.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Thank you for the opportunity to review manuscript ID bmjopen-2018-026604, entitled, Open-label dose-extending placebos for opioid use disorder: a protocol for a randomized controlled trial. This manuscript describes an ethical and well-designed study to assess the effectiveness of a dose-extending placebo as a novel and potentially effective adjunct treatment for OUD. The background, conceptualization, and description of procedures are excellent. Figure 1 is very helpful. The paper is very well organized and the writing is clear and concise. I have only minor comments.

1. It may be important to briefly mention the clinical criteria (e.g. patient subjective mood, craving, substance use) that blinded clinicians will use to determine the need for dose escalation at week 3. This clinical decision determines the final maintenance dose (i.e. dependent variable). Evaluating these criteria through chart review at the trial's conclusion may be important for understanding which clinical criteria most influenced dose escalation - and possibly shed light on the underlying mechanism for placebo. If treatment providers are required to interact with research subjects or nursing staff in order to evaluate the need for dose escalation, it could lead to unblinding.

We thank the reviewer for his very positive feedback. We agree that we did not give the readers sufficient understanding of how methadone dose adjustments are determined in our clinic. We have addressed this missing information in a new section under Study Design and Procedures entitled "Blinding."

2. Page 7; What is "Bayesian brain function"?

We have removed unnecessary reference to this term as we agree that without context, it is confusing.

3. Page 6; "raisk" should be "risk".

This typo has been corrected.

4. Page 7; "insert" should be "inert"

This typo has been corrected.

5. Page 8; Line 52. The first part of this sentence states "the placebo intervention will enhance MMT outcomes…" I'm not sure this is consistent with what the authors have written previously. It may be more accurate to write, "…the placebo intervention will achieve equivalent MMT outcomes (decreased positive urine screens and increased treatment retention) at lower mean doses of methadone.

Thank you for the suggestion to clarify; we have changed this sentence to reflect the fact that in addition to the hypothesized impact of PDE on methadone dose (primary outcome), we also anticipate that the PDE intervention will have a significant impact on outcomes associated with methadone treatment; namely, treatment retention and objective (urine screens) and subjective (self-report) measures of participant drug use while they are enrolled in methadone treatment (secondary outcomes).

Reviewer: 2

1. Burden of disease: it would be helpful to know the average doses of methadone in their treatment program - are high doses really an issue? Moreover, there is some controversy over whether QT prolongation is dose dependent and, more importantly, if the clinical outcome (rather than the proxy measure of QT prolongation) of Torsades de Pointes is dose dependent. I think the authors should present some evidence on present day programs having high average methadone doses and on if keeping doses lower really does prevent Torsades.

We thank the reviewer for the concern, and realize that perhaps the intention of our study, which is to enhance methadone treatment outcomes, was not communicated sufficiently. We do cite evidence to suggest that higher doses of methadone may be a significant reason for treatment attrition10 and may put MAT patients at higher risk for cardiotoxicity11-13. This risk would be mitigated if equivalent treatment outcomes could be achieved at lower doses of methadone. We suggest that all things being equal (i.e., non-inferior outcomes), lower levels of any medication, including methadone, would be preferred by a treating clinician. So, we chose to focus on three-month methadone dose (in milligrams) as a straight-forward, quantifiable primary outcome that might be different between the treatment arms. This said, however, it is not the explicit aim of our intervention to decrease methadone doses in our clinic. Instead, we are testing the notion that placebo effects may be used as an effective adjunct to methadone treatment to enhance treatment outcomes—of which, lower methadone dose (as a function of minimized methadone dose escalation) might be just one. Indeed, we are open to the fact that the placebo adjunct could yield therapeutic benefits on treatment retention and on in-treatment drug use. Thus, we are collecting retention data for our participants as well as indicators of drug use that include urine toxicology screening and participant self-reported drug use. To help clarify this subtle (but important) distinction in the aims of our study, we have added a sentence to the end of the third paragraph in the Introduction, as well as to the Objectives section of the manuscript.

2. I am concerned about the study design with respect to the use of placebo and blinding: in this case the participants will know which group they are assigned to and the subjective fear they have of their opioid dose not being high enough is not addressed - they will know that the dose extending pill that they are receiving is a placebo and this will still factor into their subjective withdrawal symptoms and requests for a higher dose.

Addressed below

3. Finally, it is hard to understand how their treating clinicians would not become aware of the participants' study assignment: surely the clinicians will hear from their patients about the dose extenders and so it cannot really be single-blind. Finally, clinicians will have a plethora of clinical experience in treating opioid use disorder patients with methadone and have some preconceptions of reasonable therapeutic dose ranges of methadone. If they are presented with a patient on a low dose of methadone with mild subjective withdrawal symptoms they may be more likely to increase the dose based purely on the low dose and previous clinical experience that most of their patients do well on higher doses. It seems that the only thing that could really get at the answer the authors are seeking is to keep participants blind to their methadone dose altogether and have dose increases made only by a preset protocol using a threshold score on a subjective withdrawal symptom scale.

We thank the reviewer for her clear insight on the problem of blinding. As mentioned above, we feel that the information that was previously provided in the earlier version of this manuscript was insufficient for a reader's understanding of how dose alterations are managed in our clinic. To address this gap, we have added a new section under Study Design and Procedures entitled "Blinding" that addresses how we are handling clinician, participant and physician blinding methods.

VERSION 2 – REVIEW

REVIEWER	Gabriel Culbert, Assistant Professor Health Systems Science, University of Illinois at Chicago (UIC) College of Nursing, Chicago, IL< USA
REVIEW RETURNED	13-Mar-2019

GENERAL COMMENTS	The authors have satisfactorily addressed my previous comments. In particular, the description of blinding procedures is thorough and helpfully resolves previous concerns. This reviewer is not convinced that unblinding will be a rare occurrence (specifically unblinding that occurs during patients' face-to face meetings with their healthcare providers) and it will be important for the researchers to monitor and record unblinding that occurs in the study. To prevent bias, dosing decisions should be made according to a clear protocol or algorithm irrespective of the patient's treatment allocation. The authors discuss "myriad variables that determine methadone dose changes", yet a better understanding and some control over how these variables inform treatment decisions (i.e. dose escalation) will be important for interpreting the results of this trial. Some concerns remain about language such as "enhance outcomes of methadone treatment…" (p.10), which seem to suggest that PDE may prove superior to TAU with respect to MMT outcomes. Why, for example, would we expect increased treatment retention from participants receiving PDE? Are higher methadone doses that PDE will prevent a main reason for attrition from methadone? It seems rather that the aim of the study is to demonstrate equivalence - i.e. the PDE intervention will achieve equivalent MMT outcomes (e.g. negative urine drug screens, retention) at a lower mean dose of methadone.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1 Comments to Author:

Reviewer Comment #1: The authors have satisfactorily addressed my previous comments. In particular, the description of blinding procedures is thorough and helpfully resolves previous concerns. This reviewer is not convinced that unblinding will be a rare occurrence (specifically unblinding that occurs during patients' face-to face meetings with their healthcare providers) and it will be important for the researchers to monitor and record unblinding that occurs in the study. To prevent bias, dosing decisions should be made according to a clear protocol or algorithm irrespective of the patient's treatment allocation. The authors discuss "myriad variables that determine methadone dose changes", yet a better understanding and some control over how these variables inform treatment decisions (i.e. dose escalation) will be important for interpreting the results of this trial.

Author Response: Thank you. We appreciate that significant information was omitted which we believe, now added, addresses the reviewer's concerns. This new text can be found under the section in the manuscript entitled "Blinding":

Blinding. Clinic staff are independent of the research study implementation. Correspondingly, members of the study team responsible for administration of assessments, delivery of placebo pills or data analysis play no role in dose increase/decrease determinations. Methadone dose adjustments

are made based on two criteria: (1) scores on a validated subjective withdrawal symptom checklist and (2) treatment team consensus. (1) The Subjective Opioid Withdrawal Scoring (SOWS) system is an assessment of the severity of symptoms of withdrawal and is delivered outside of the study frame (the SOWS measurements that are obtained as part of the baseline, 2-week and 1-, 2- and 3-month study team meetings are distinct, kept separate from the clinical SOWS assessment for dose change determination). All patients in the clinic are asked to submit their responses on this checklist at a time point corresponding with their achievement of an initial stabilization dose, generally 2-4 weeks post-entry into treatment. This assessment is considered as one factor in dose change determinations. (2) Treatment teams meet weekly to discuss individual patients' progress, and consensus must be obtained between the treating physician, the counselor and the nurse practitioner (NP) to recommend a dose increase. Primary goals in increasing the methadone dose include suppression of withdrawal symptoms, tempering of intrusive drug cravings, and agonist blockade. Physicians and the NP evaluate and document the relative risks and benefits of any proposed dosage change, with attention paid to several factors including over-sedation, drug-drug interactions, cardiac side effects, and adherence to daily treatment. Treating physicians and the NP, including the facility's Medical Director (AG) are all blind to study enrollment and randomization. Patient study participation is not discussed during treatment team meetings, and the counselors, NP and physicians are asked not to probe patients about their involvement and experience with the study. Thus, it is unlikely that a physician or NP would become unblinded to treatment allocation. Regardless, given the myriad variables that determine methadone dose changes, it is unlikely that this knowledge would factor in the calculus of whether to make a dose adjustment, as the clinic's standard of care dictates that the participant's well-being is the primary consideration in any clinical course of action. If, however, a physician or the NP becomes unblinded to a patient's study treatment allocation, they are asked to communicate that to a member of the study team.

Reviewer Comment #2: Some concerns remain about language such as "enhance outcomes of methadone treatment…" (p.10), which seem to suggest that PDE may prove superior to TAU with respect to MMT outcomes. Why, for example, would we expect increased treatment retention from participants receiving PDE? Are higher methadone doses that PDE will prevent a main reason for attrition from methadone? It seems rather that the aim of the study is to demonstrate equivalence - i.e. the PDE intervention will achieve equivalent MMT outcomes (e.g. negative urine drug screens, retention) at a lower mean dose of methadone.

Author response: Thank you; indeed, this is a non-inferiority test. We have changed the language in this problematic section to clarify this:

Specifically, we hypothesize that an open-label placebo dose-extension paradigm (PDE) will obviate higher-dose methadone treatment for a significant portion of new initiates and will thereby reduce methadone-associated side effects, with no concomitant change in outcomes such as treatment retention, drug use, self-reports and clinical observations of withdrawal, craving or quality of life.

VERSION 3 - REVIEW

REVIEWER	Gabriel J. Culbert University of Illinois at Chicago, U.S.A.
REVIEW RETURNED	18-Apr-2019

GENERAL COMMENTS	Thank you. The authors have thoughtfully and thoroughly addressed previous concerns. Specifically, they have provided a detailed explanation of assessments and procedures for determining dose escalation, and clarified the language regarding expected outcomes to make it consistent with the overall aims and study design. Well done!