PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

Identifying priorities for future research on reducing and stopping psychiatric medication: Results of a James Lind Alliance priority setting partnership

Authors

Boland, Miriam; Higgins , Agnes; Beecher, Claire; Bracken, Pat; Burn, Wendy; Cody, Anne; Framer, Adele; Gronlund, Toto; Horowitz, Mark; Huff, Christy; Jayacodi, Sandra; Keating, Dolores; Kessler, David; Konradsson Geuken, Åsa; Lamberson, Nicole; Montagu, Luke; Smith, Ruth; Cadogan, Cathal

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Bethell, Jennifer**
Affiliation	**Toronto Rehabilitation Institute, Research**
Date	**31-May-2024**
COI	**none.**

Thank-you for the opportunity to review this paper. The authors have used an established methodology – a James Lind Alliance Priority-Setting Partnership – to establish priorities for research related to reducing and stopping psychiatric medication from the perspectives of: (1) people with lived experience of taking and/or stopping psychiatric medication, (2) family members/carers/supporters, and (3) healthcare professionals.

The paper is very clear, well-written and gives a comprehensive account of the process. I have only minor suggestions:

[1] Background: the statement “Reasons for wanting to discontinue psychiatric medication include adverse effects, the desire to recapture personal autonomy, and to live a life free of medication.” – what about lack of perceived benefit?

[2] Methods/Results: the proportion of responses by stakeholder group added to 100% - people with lived experience (69%), healthcare professionals (21%), family members/carers/supporters (10%). Does this mean individuals were required to select only

one perspective? The overlap (i.e., “dual roles”) is mentioned in the context of the steering group. Please describe how it was treated in the data collection.

[3] Results: Revise slightly name of table 3 to indicate the numbers are referring to the number of summary questions (?) – without text, it is unclear what the numbers in the cells are referring to. Current title: "Table 3: Overview of process of iterative review and refinement of summary questions following Round 1 survey”

[4] Methods/Limitations: there is no data reported with respect to diversity of sample relating to race, ethnicity and other demographic factors. This has been a limitation of previous PSPs. There is only passing mention that “… due to resource and logistical constraints…..limited accessibility for certain groups and countries.” Please indicate if these data were not collected and why.

Reviewer	**2**
Name	**Groot, Peter C**
Affiliation	**UMC Utrecht**
Date	**03-Jun-2024**
COI	**I am involved in the development and reasearch of tapering strips but not in any way in the production or sale of tapering strips. In the Netherlands, tapering medications are made, at the specific request of the not-for-profit foundation Cinderella Therapeutics, by the Regenboog pharmacy in Bavel, The Netherlands, against a nationally pre-set, regulated reimbursement. Other pharmacies in the Netherlands do not produce tapering strips as the pre-set reimbursement is considered too low. The User Research Centre at UMC Utrecht has benefitted from an educational grant provided by the Regenboog Pharmacy.**

Boland et al. conducted a thorough search to help set priorities for future research on reducing and stopping psychiatric medication. I believe the method used is sound, the study was carried out with great care, and it deserves to be published. However, I have 2 remarks and advise that the discussion includes more about the following issues, as this may help set up better studies in the future.

- - - - - 1) One relevant and important question posed in the study is: "What are the positive and negative long-term consequences of reducing and stopping psychiatric medication on an individual’s physical and mental health status?" (Table 5, nr 6). I find this question confusing because the outcomes of stopping the same prescription drug can vary widely. For example, the same persons might become psychotic, violent, or suicidal if they stop abruptly, but could remain problem-free for years if they taper gradually. I experienced this myself when

tapering an antidepressant in 2012 and 2023 (1). This implies that the answer to the question depends on how gradually a person can taper. It hinges on how the question is formulated. There is no single right answer, and this ambiguity can be a handicap for setting up future studies if it is not made explicit from the beginning. Because this could easily lead to unhelpful discussions and unnecessary confusion, making it harder to design effective studies to address important questions. To prevent this, I suggest explicitly making this point in the discussion and perhaps also revisiting the formulation of the Top 10 issues that have been identified.

- - - - - 2) It continues to surprise me that, also in this study, almost everyone who advocates for safer and more gradual tapering sees the lack of lower dosages as one of the bigger unmet needs requiring urgent solutions. I disagree. In the Netherlands, accurately determined lower dosages in tablet form are already available in tapering strips (2-5) for more than 50 different prescription drugs, including 21 antidepressants, 13 antipsychotics, 12 benzodiazepines, and 4 opioid painkillers (2). Using tapering strips, GPs and psychiatrists can conveniently and easily prescribe any tapering schedule they wish for a patient. As explained in the new Maudsley Deprescribing Guidelines off-label prescribing of tapering medication in tapering strips is permissible in the Netherlands, as well as in many other countries (8).

In Holland prescribing tapering strips is becoming routine for a growing number of GPs and psychiatrists. Despite this, many patients have to cover part or all of the cost themselves, depending on their health insurer. Their biggest unmet need is the lack of reimbursement, not the lack of lower dosages. Addressing this unmet need is straightforward and could be achieved at any moment, the only requirement being full reimbursement, regardless of whether lower dosages needed for safe tapering are provided in tapering strips or by any other means.

Reimbursement is not a scientific issue, but a societal one. If reimbursement is arranged, other practical solutions for obtaining lower dosages will be resolved quickly enough thereafter. Without reimbursement, we will continue struggling for years to come. For this reason, I find the word "ultimately" in the last sentence of the conclusion a bit defeatist: "with a view to ultimately improving the future health and well-being of individuals who are taking psychiatric medication." When there is the will, things can be improved much more quickly. - - - - - -

(1) Groot, PC (2024). Tapering strips: a practical tool for personalised and safe tapering of withdrawal-causing prescription drugs. Mad in America, April 9. https://www.madinamerica.com/2024/04/tapering-strips-a-practical-tool-for-personalised-and-safe-tapering-of-withdrawal-causing-prescription-drugs/

(2) Groot PC, van Os J. How user knowledge of psychotropic drug withdrawal resulted in the development of person-specific tapering medication. Therapeutic advances in psychopharmacology. 2020;10. https://doi.org/10.1177/2045125320932452

(3) Groot PC, van Os J. Antidepressant tapering strips to help people come off medication more safely. Psychosis. 2018;10. https://doi.org/10.1080/17522439.2018.1469163

10.1080/17522439.2018.1469163

(4) Groot PC, van Os J. Outcome of Antidepressant Drug Discontinuation with Taperingstrips after 1-5 Years. Therapeutic advances in psychopharmacology. 2020;10. https://doi.org/10.1177/2045125320954609

(5) Groot PC, van Os J. Successful use of tapering strips for hyperbolic reduction of antidepressant dose - a cohort study. Therapeutic advances in psychopharmacology. 2021;11. https://doi.org/10.1177/20451253211039327

(6) van Os J, Groot PC. Outcomes of hyperbolic tapering of antidepressants. Therapeutic advances in psychopharmacology. 2023;13. https://doi.org/10.1177/20451253231171518

(7) https://www.taperingstrip.com/prescribing-and-ordering/

(8) Horowitz, M., & Taylor, D. (2024). The Maudsley Deprescribing Guidelines: Antidepressants, Benzodiazepines, Gabapentinoids and Z-drugs (1st ed). Wiley Blackwell.

VERSION 1 - AUTHOR RESPONSE

bmjopen-2024-088266 - "Identifying priorities for future research on reducing and stopping psychiatric medication: Results of a James Lind Alliance priority setting partnership"

We would like to thank the reviewers for reviewing our manuscript and for the feedback they have provided. We have responded to each comment below and revised the manuscript accordingly.	
Reviewer #1 Comments	**Responses**

The paper is very clear, well-written and gives a comprehensive account of the process. I have only minor suggestions:	We are very grateful to the reviewer for reviewing our manuscript and for the feedback they have provided. We have responded to each comment below and revised the manuscript accordingly. We have indicated the page numbers within the revised manuscript where revisions have been made (all visible as tracked changes).
Background: the statement "Reasons for wanting to discontinue psychiatric medication include adverse effects, the desire to recapture personal autonomy, and to live a life free of medication." – what about lack of perceived benefit?	We have now acknowledged the lack of perceived benefits in the sentence below and included an additional reference. *"Reasons for wanting to discontinue psychiatric medication include adverse effects, lack of perceived benefit, the desire to recapture personal autonomy, and to live a life free of medication."* (7-9) [Page 5]
Methods/Results: the proportion of responses by stakeholder group added to 100% - people with lived experience (69%), healthcare professionals (21%), family members/carers/supporters (10%). Does this mean individuals were required to select only one perspective? The overlap (i.e., "dual roles") is mentioned in the context of the steering group. Please describe how it was treated in the data collection.	Yes, survey respondents were asked to select the single stakeholder group that best represented them and informed their responses. We have clarified this in the text of the methods section relating to each of the two surveys as per below. *"In cases where respondents could identify with more than one stakeholder group, they were asked to select the group that best reflected their questions/uncertainties about reducing and stopping psychiatric medication. For example, if a healthcare professional also had lived experience of discontinuing a psychiatric medication, and their questions stemmed from their lived experience as opposed to their clinical/professional experience, then they were advised to select 'people with lived experience of taking and/or stopping psychiatric medication' as their respondent group."* (page 10)

	"Similar to the Round 1 survey, in cases where respondents could identify with more than one stakeholder group, they were asked to select the group that best reflected their questions/uncertainties about reducing and stopping psychiatric medication." (page 12)
Results: Revise slightly name of table 3 to indicate the numbers are referring to the number of summary questions (?) – without text, it is unclear what the numbers in the cells are referring to. Current title: "Table 3: Overview of process of iterative review and refinement of summary questions following Round 1 survey"	Thank you for your suggestion. We have now incorporated "Number of summary questions per round of review" into the table to make it clearer what the numbers in the cells are referring to. We have also replaced the word "Round" in the table with "Review" to avoid any confusion with the two surveys. (Page 22)
Methods/Limitations: there is no data reported with respect to diversity of sample relating to race, ethnicity and other demographic factors. This has been a limitation of previous PSPs. There is only passing mention that "… due to resource and logistical constraints….. limited accessibility for certain groups and countries." Please indicate if these data were not collected and why.	There were four demographic questions included in both surveys. These questions related to stakeholder group, age, gender, and country of origin and this is now detailed in the methods section. *"The survey also asked respondents to provide some brief demographic information in terms of stakeholder group, age, gender, and country of origin."* (page 10) No questions relating to race or ethnicity were asked. We have expanded on this in the limitations section as per the text below. *"A limitation of this study was that it was conducted entirely through English and the two surveys were only available in digital format due to resource and logistical constraints. This may have limited*

	accessibility for certain groups and countries where English is not widely spoken. Furthermore, in consultation with the Steering Group, it was decided not to capture information on the ethnicity of survey respondents as this information would not have contributed directly to the selection of the Top 10 list of research priorities." (page 32)
Reviewer #2 Comments	
Boland et al. conducted a thorough search to help set priorities for future research on reducing and stopping psychiatric medication. I believe the method used is sound, the study was carried out with great care, and it deserves to be published. However, I have 2 remarks and advise that the discussion includes more about the following issues, as this may help set up better studies in the future.	We are very grateful to the reviewer for reviewing our manuscript and for the positive feedback they have provided.
One relevant and important question posed in the study is: "What are the positive and negative long-term consequences of reducing and stopping psychiatric medication on an individual's physical and mental health status?" (Table 5, nr 6). I find this question confusing because the outcomes of stopping the same prescription drug can vary widely. For example, the same persons might become psychotic, violent, or suicidal if they stop abruptly, but could remain problem-free for years if they taper gradually. I	We are grateful to the reviewer for sharing their personal experience of tapering psychiatric medication. While we are grateful to the reviewer for providing their feedback on the questions, the process of formulating the Top 10 questions, as detailed in the manuscript, followed the James Lind Alliance methodology. Questions submitted to the Round 1 survey underwent an extensive process of data analysis to produce a list of summary questions. The exact wording of each summary question was finalised through several rounds of review and refinement

experienced this myself when tapering an antidepressant in 2012 and 2023 (1). This implies that the answer to the question depends on how gradually a person can taper. It hinges on how the question is formulated. There is no single right answer, and this ambiguity can be a handicap for setting up future studies if it is not made explicit from the beginning. Because this could easily lead to unhelpful discussions and unnecessary confusion, making it harder to design effective studies to address important questions. To prevent this, I suggest explicitly making this point in the discussion and perhaps also revisiting the formulation of the Top 10 issues that have been identified.	amongst the Steering Group which consisted of people with lived experience of taking and/or stopping psychiatric medication, family members and/or carers/supporters, and healthcare professionals. The James Lind Alliance methodology does not permit any subsequent changes to the questions once the PSP study has concluded. We respectfully disagree with the reviewer's opinion that any of the questions imply a particular answer. It is only through future research that the questions that have been identified, which have already been checked against existing evidence (as per Step 4 of the PSP process), can be answered.
It continues to surprise me that, also in this study, almost everyone who advocates for safer and more gradual tapering sees the lack of lower dosages as one of the bigger unmet needs requiring urgent solutions. I disagree. In the Netherlands, accurately determined lower dosages in tablet form are already available in tapering strips (2-5) for more than 50 different prescription drugs, including 21 antidepressants, 13 antipsychotics, 12 benzodiazepines, and 4 opioid painkillers (2). Using tapering strips, GPs and psychiatrists can conveniently and easily prescribe any tapering schedule they	We are grateful to the reviewer for sharing their previous publications on tapering strips and offering potential solutions to overcome some of the issues that are faced by individuals who are tapering psychiatric medication. The point about availability of lower dosage forms appears not to have been interpreted correctly. We have referred to the perceived need among our study's respondents to improve availability of lower dosages (as opposed to them not being available) which is essentially the point that the reviewer has made:

wish for a patient. As explained in the new Maudsley Deprescribing Guidelines off-label prescribing of tapering medication in tapering strips is permissible in the Netherlands, as well as in many other countries (8). In Holland prescribing tapering strips is becoming routine for a growing number of GPs and psychiatrists. Despite this, many patients have to cover part or all of the cost themselves, depending on their health insurer. Their biggest unmet need is the lack of reimbursement, not the lack of lower dosages. Addressing this unmet need is straightforward and could be achieved at any moment, the only requirement being full reimbursement, regardless of whether lower dosages needed for safe tapering are provided in tapering strips or by any other means. Reimbursement is not a scientific issue, but a societal one. If reimbursement is arranged, other practical solutions for obtaining lower dosages will be resolved quickly enough thereafter. Without reimbursement, we will continue struggling for years to come. For this reason, I find the word "ultimately" in the last sentence of the conclusion a bit defeatist: "with a view to ultimately improving the future health and well-being of individuals who are	*"….the question about improving the availability of psychiatric medication in formulations and dosage ranges that facilitate the tapering process was deemed a key uncertainty among many survey respondents and workshop participants."* (page 31) We have expanded briefly on the point about availability and reimbursement of tapering strips outside the Netherlands as follows: *"…outside the Netherlands, tapering strips are not widely available or accessible on public health schemes via existing reimbursement mechanisms."* (page 32) We acknowledge the great deal of research that the reviewer has conducted in this space. We have cited two of the reviewer's previous publications in the manuscript, references 26: Groot PC, van Os J. How user knowledge of psychotropic drug withdrawal resulted in the development of person-specific tapering medication. Therapeutic Advances in Psychopharmacology. 2020;10:2045125320932452. and 39: Groot PC, van Os J. Successful use of tapering strips for hyperbolic reduction of antidepressant dose: A cohort study. Therapeutic Advances in Psychopharmacology. 2021;11:20451253211039327. In response to the reviewer's feedback the word "ultimately" has been removed from the conclusion. It now reads as follows: "*This Top 10 list of research priorities is relevant to research funding agencies and could help to guide*

taking psychiatric medication." When there is the will, things can be improved much more quickly.	*future research and deliver responsive and strategic allocation of research resources, with a view to improving the future health and well-being of individuals who are taking psychiatric medication."* (Page 31).

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Bethell, Jennifer**
Affiliation	**Toronto Rehabilitation Institute, Research**
Date	**26-Aug-2024**
COI	**none**

Thank you for your thoughtful consideration of the comments and revisions to the paper.

My remaining query relates to the revision for the final comment (relating to collection of data on race or ethnicity). The revision is noted by the authors for the discussion: "...it was decided not to capture information on the ethnicity of survey respondents as this information would not have contributed directly to the selection of the Top 10 list of research priorities." However, it is not clear that the demographic information that was captured (i.e., age, gender, country of origin) was used to select the top 10 either. Of course, respondent burden and appropriate measures for data collection are always concerns for the steering group in designing the questionnaires. Suggest that perhaps the rationale for the selection of the demographic questions that were chosen could be described with a very brief rational as a design decision (in the methods section), including if/how they were used to select the top 10, and then briefly touched on the associated limitations (in the discussion).

Reviewer	**2**
Name	**Groot, Peter C**
Affiliation	**UMC Utrecht**
Date	**02-Sep-2024**

COI Competing InterestsPeter C. Groot was involved in the development of tapering strips and investigates their use in daily clinical practice. He is not involved in any way in their production or sales. In the Netherlands, tapering medications are made, at the specific request of the not-for-profit foundation Cinderella Therapeutics, by the Regenboog pharmacy in Bavel, The Netherlands, against a nationally pre-set, regulated reimbursement. Other pharmacies in the Netherlands do not produce tapering strips as the pre-set reimbursement is considered too low. The User Research Centre at UMC Utrecht has benefitted from an educational grant provided by the Regenboog Pharmacy.

I thank the authors for their response to my review, about which I have the following remarks:

The authors state that they 'disagree with the reviewer's opinion that any of the questions imply a particular answer.' I object to this interpretation of my feedback because I suggested the exact opposite: that answers to questions about experienced withdrawal will vary significantly depending on how gradually a person can, or is allowed to, taper. The answer will therefore NOT be one particular answer, which would be fine, but may be completely different answers, depending on how gradual this person was able to taper.

This variability in answer from the same persons was observed in two observational studies involving over 1,100 participants (Groot & Van Os 2018, 2021). In these studies, participants compared the severity of experienced withdrawal during previous failed tapering attempts with those experienced during a new attempt, using one or more tapering strips. The difference was substantial: the mean severity of reported withdrawal, on a Likert scale of 1-7, was 6.1 and 6.0 for the failed attempts, compared to 3.2 and 3.1 for the tapering attempts using tapering strips, which allowed 70% of the participants using the tapering strips to taper completely.

These very different outcomes, within the same group, can only be meaningfully interpreted by considering the quality of the tapering process, a factor often overlooked in existing withdrawal literature, but crucial for future studies. To avoid future confusion, it is important to explicitly acknowledge that experienced withdrawal is not a fixed characteristic of a person, but a measure that can be expected to improve when patients are allowed to taper more gradually. Therefore, future scientific studies can only compare reported withdrawal experiences meaningfully if they account for the quality (graduality and duration) of the taper. I consider it important that this consideration be explicitly addressed in the design of new withdrawal studies and find it regrettable that the current manuscript does not explicitly touch upon this.

The authors discuss the lack of evidence regarding the efficacy of using existing formulations for tapering and then fail to mention that the efficacy of tapering strips in clinical practice has been investigated in 4 observational studies, with over 2,700 participants (Groot & Van

Os 2018, 2020, 2021; Van Os & Groot, 2023). This important factual information should not be omitted, especially considering that these studies are, to my knowledge, the only published studies in which tapering using much more gradual tapering schedules than those routinely prescribed in clinical practice has been systematically investigated in a large group of people.

The authors briefly touch on the availability and reimbursement of tapering strips outside the Netherlands, stating: '…outside the Netherlands, tapering strips are not widely available (…) via existing reimbursement mechanisms.' However, this statement is factually incorrect, as in the Netherlands, most health insurers still do not reimburse tapering strips. Discussions on their reimbursement have been ongoing for over eight years now. Therefore, it would be more accurate to write '…as in the Netherlands,' rather than '…outside the Netherlands.'

The authors acknowledge the 4 observational studies that have been done and note that they have cited one review and one observational study. However, I find referencing only one of four relevant observational studies, all of which are crucial to the study of withdrawal, to be selective reporting that is not justified. To ensure factually correct information, I suggest the following changes to the text beginning with 'Tapering strips, consisting of…' and ending with '…or accessible on public health schemes':

'In the Netherlands, tapering strips have been developed, consisting of psychiatric medication packaged into pouches of individual daily doses, to enable gradual dosage reduction. Their efficacy has been investigated in three retrospective observational studies and one prospective observational study, involving over 2,700 participants (Groot & Van Os 2018, 2020, 2021; Van Os & Groot, 2023). While tapering strips can be prescribed off-label, for most patients they are not yet available through existing reimbursement mechanisms in the Netherlands or other countries, which remains an important issue to resolve.

References:

Groot PC, van Os J. Antidepressant tapering strips to help people come off medication more safely. Psychosis. 2018;10. 10.1080/17522439.2018.1469163

Groot PC, van Os J. Outcome of Antidepressant Drug Discontinuation with Taperingstrips after 1-5 Years. Therapeutic advances in psychopharmacology. 2020;10:2045125320954609

Groot PC, van Os J. Successful use of tapering strips for hyperbolic reduction of antidepressant dose - a cohort study. Therapeutic advances in psychopharmacology. 2021;11:20451253211039327

van Os J, Groot PC. Outcomes of hyperbolic tapering of antidepressants. Therapeutic advances in psychopharmacology. 2023;13:10.1177/20451253231171518

VERSION 2 - AUTHOR RESPONSE

bmjopen-2024-088266.R1 - "Identifying priorities for future research on reducing and stopping psychiatric medication: Results of a James Lind Alliance priority setting partnership"

We would like to thank the reviewers for reviewing our manuscript and for the feedback they have provided. We have responded to each comment below and revised the manuscript accordingly.

Reviewer 1

Reviewer comment: My remaining query relates to the revision for the final comment (relating to collection of data on race or ethnicity). The revision is noted by the authors for the discussion: "...it was decided not to capture information on the ethnicity of survey respondents as this information would not have contributed directly to the selection of the Top 10 list of research priorities." However, it is not clear that the demographic information that was captured (i.e., age, gender, country of origin) was used to select the top 10 either. Of course, respondent burden and appropriate measures for data collection are always concerns for the steering group in designing the questionnaires. Suggest that perhaps the rationale for the selection of the demographic questions that were chosen could be described with a very brief rational as a design decision (in the methods section), including if/how they were used to select the top 10, and then briefly touched on the associated limitations (in the discussion).

Author response: Thank you for your query. To clarify, the demographic information that was captured in terms of respondents' age, gender and country of origin was not used in selecting the Top 10 priorities. It is standard practice in JLA priority setting partnerships to ask survey respondents to provide some brief demographic information, but only the breakdown of responses across different stakeholder groups is taken into consideration during the shortlisting of summary questions during Step 5 (Interim prioritisation - Round 2 survey). We have clarified this in the manuscript as follows through revisions to the following parts of the methods section:

Step 2: “There are no formal target sample sizes for PSP surveys.(18) However, balanced representation of all stakeholder groups and diversity of respondents is desirable. Respondents’ demographic profile was monitored on a weekly basis, primarily in terms of stakeholder group. Various strategies were implemented to enhance engagement from specific stakeholder groups, including targeted posts on Twitter and requesting assistance from specific organisations and groups in disseminating study information within their networks.” [page 8]

Step 5: “Using the demographic information submitted by respondents, responses were grouped for each stakeholder group, and the questions were ranked based on the frequency with which they had been selected. This enabled the ranked priorities across the different stakeholder groups to be compared and contrasted. Once the analysis was complete, the Steering Group reviewed the findings and the 19 most highly ranked questions across the three key stakeholder groups were taken forward to the final workshop (Step 6).” [page 11]

Reviewer 2

Reviewer comment: The authors state that they 'disagree with the reviewer’s opinion that any of the questions imply a particular answer.' I object to this interpretation of my feedback because I suggested the exact opposite: that answers to questions about experienced withdrawal will vary significantly depending on how gradually a person can, or is allowed to, taper. The answer will therefore NOT be one particular answer, which would be fine, but may be completely different answers, depending on how gradual this person was able to taper.
This variability in answer from the same persons was observed in two observational studies involving over 1,100 participants (Groot & Van Os 2018, 2021). In these studies, participants compared the severity of experienced withdrawal during previous failed tapering attempts with those experienced during a new attempt, using one or more tapering strips. The difference was substantial: the mean severity of reported withdrawal, on a Likert scale of 1-7, was 6.1 and 6.0 for the failed attempts, compared to 3.2 and 3.1 for the tapering attempts using tapering strips, which allowed 70% of the participants using the tapering strips to taper completely.

These very different outcomes, within the same group, can only be meaningfully interpreted by considering the quality of the tapering process, a factor often overlooked in existing withdrawal literature, but crucial for future studies. To avoid future confusion, it is important to explicitly acknowledge that experienced withdrawal is not a fixed characteristic of a person, but a measure that can be expected to improve when patients are allowed to taper more gradually. Therefore, future scientific studies can only compare reported withdrawal experiences meaningfully if they account for the quality (graduality and duration) of the taper. I consider it important that this consideration be explicitly addressed in the design of new withdrawal studies and find it regrettable that the current manuscript does not explicitly touch upon this.

Author response: The focus of this manuscript is not to speculate on the answers to the questions that have been identified through the priority setting partnership methodology that we used, but to present them to the journal's readership and detail how they were developed. As detailed in the manuscript, the questions were based on over 3500 unique questions submitted by close to 900 respondents. Following a long and detailed analytical process that was overseen by our Steering Group consisting of key stakeholders internationally representing people with lived experience, family members/carers and healthcare professionals, these questions have been checked against existing evidence (as per Step 4 of the PSP process) and sufficiently high-quality evidence to address them was not identified. We are very keen to respect this process and the efforts of all involved, particularly the participants. We feel strongly that to begin speculating on the answers to any of the questions that have been reviewed in detail through this process would not be appropriate within our manuscript as it would undermine the need for further research in addressing the Top 10 priorities.

Different researchers will have different approaches and interpretations on how best to address the priorities, but it is not within the scope of this manuscript and the methodology that we used to direct how this should be done. As detailed in our paper, and in accordance with the James Lind Alliance, the only evidence that is considered sufficiently high quality to answer any of the questions involves systematic reviews published within the last three years (Step 4 of the PSP process). Evidence of sufficient quality was not found to answer the questions that are presented in our manuscript. Therefore, while interesting, the reviewer's

studies did not meet the relevant evidence threshold. It is only through future research that the questions that have been identified, which have already been checked against existing evidence can be answered. We do hope the reviewer may consider writing their own response to the Top 10 priorities once published and stimulate further discussions on tapering within the literature.

Reviewer comment: The authors discuss the lack of evidence regarding the efficacy of using existing formulations for tapering and then fail to mention that the efficacy of tapering strips in clinical practice has been investigated in 4 observational studies, with over 2,700 participants (Groot & Van Os 2018, 2020, 2021; Van Os & Groot, 2023). This important factual information should not be omitted, especially considering that these studies are, to my knowledge, the only published studies in which tapering using much more gradual tapering schedules than those routinely prescribed in clinical practice has been systematically investigated in a large group of people.

Author response: We hope that the response to the previous comment above will help the reviewer to better understand PSP methodology and why studies such as their own did not meet the threshold for addressing the uncertainties that have been identified and that it is beyond the scope of the paper and study to cite every research study we located when we completed our review of evidence.

Reviewer comment: The authors briefly touch on the availability and reimbursement of tapering strips outside the Netherlands, stating: '…outside the Netherlands, tapering strips are not widely available (…) via existing reimbursement mechanisms.' However, this statement is factually incorrect, as in the Netherlands, most health insurers still do not reimburse tapering strips. Discussions on their reimbursement have been ongoing for over eight years now. Therefore, it would be more accurate to write '…as in the Netherlands,' rather than '…outside the Netherlands.'

Author response: Thank you. We have updated this sentence accordingly.

“Tapering strips, consisting of psychiatric medication packaged into pouches of individual daily doses, have been developed in the Netherlands to enable gradual dosage reduction.(39)

However, as in the Netherlands, tapering strips are not widely available or accessible on public health schemes via existing reimbursement mechanisms."

Reviewer comment: The authors acknowledge the 4 observational studies that have been done and note that they have cited one review and one observational study. However, I find referencing only one of four relevant observational studies, all of which are crucial to the study of withdrawal, to be selective reporting that is not justified. To ensure factually correct information, I suggest the following changes to the text beginning with 'Tapering strips, consisting of…' and ending with '…or accessible on public health schemes':

'In the Netherlands, tapering strips have been developed, consisting of psychiatric medication packaged into pouches of individual daily doses, to enable gradual dosage reduction. Their efficacy has been investigated in three retrospective observational studies and one prospective observational study, involving over 2,700 participants (Groot & Van Os 2018, 2020, 2021; Van Os & Groot, 2023). While tapering strips can be prescribed off-label, for most patients they are not yet available through existing reimbursement mechanisms in the Netherlands or other countries, which remains an important issue to resolve.

Author response: We admire the reviewer's previous research and all their work on trying to improve the tapering process and thank them for writing a suggested paragraph for our manuscript to showcase this work. As per our previous responses above, we have followed the evidence checking process that we outlined as part of our methodology. As this is not a paper on tapering strips, nor is it a systematic review, we do not agree with the suggestion that we are being selective in our reporting by not including the suggested paragraph.