Author's response to reviews

**Title:** Long-acting methylphenidate formulations in the treatment of attention-deficit/hyperactivity disorder: a narrative, systematic review of head-to-head studies

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**Version:** 2  **Date:** 9 August 2013

**Author's response to reviews:** see over
Dear Dr Harold,

Thank you for considering our manuscript for publication in *BMC Psychiatry*. Our responses to the reviewers’ comments are listed below, and the corresponding amendments have been tracked in the manuscript. We hope that the revised manuscript is satisfactory to you and the reviewers.

Best wishes,

Dr David Coghill

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**Editorial query**

Please could you provide a brief explaining of the use of "narrative" in the title of the manuscript. We are unclear at present what this part of the review refers to, as the manuscript appears to be a systematic review only.

**Response:**

The use of the term ‘narrative’ in the title of the manuscript reflected the qualitative, descriptive nature of the review, and the inclusion of clinical recommendations. To prevent confusion, we have removed the term ‘narrative’ from the manuscript title.

**Reviewer:** Jeffrey Newcorn

**Reviewer’s report:**

This review examines head to head comparison studies of different long-acting MPH formulations. It is comprehensive and very well done. It doesn’t yield any surprising findings,
but it provides all of what we know in one concise report. To this end, this contribution could have merit to the field. Comments by section follow. All of these comments qualify as minor essential revisions.

**Abstract.**
Summary is adequate. Conclusions section is pretty weak. Hopefully the authors can come with some more pointed conclusions as these seem to be pretty generic.

**Response**
We agree that the abstract conclusions were generic and have modified the text to highlight key findings.

**Introduction.**

**Comment 1**) Pg 7. The formulations claim to be designed to provide utility for at least 8 hours. Whether they all do is a matter of some debate in clinical circles.

**Response**
We agree with the reviewer and have modified the wording on page 7 as follows ‘The various MPH formulations use different technologies that aim to provide symptom control for at least 8 hours and also incorporate differing proportions of immediate- and extended-release MPH’

**Comment 2**) Pg 7. The d isomer of MPH may or may not be more potent – I’m not sure that’s ever been studied. It is not really active, but probably for other reasons. L-MPH is metabolized very quickly via first pass and so there is almost no circulating L-MPH in blood (unless MPH patch is used). It may or may not be taken up into brain efficiently as well. Anyway, I would say the term “potency” here is not well chosen.

**Response**
The rapid metabolism of the l-isomer has been mentioned and the reference to potency of d-MPH has been removed from the text.

**Comment 3**) Pg 7–8. I am not sure who the intended readership is. For European readers use of these brand names is fine. For compatibility with US products it would be useful to also indicate the name of the comparable formulation – e.g., metadate CD for Equasym.

**Response**
We appreciate the reviewer’s comment regarding non-European trade names and have added a note on page 7 of the manuscript to direct the reader to the information on drug name synonyms presented in Table 1. We have also included the trade name for Equasym XL in the USA (Metadate CD) in the text on page 8 of the manuscript.
Comment 4) Pg 8. I would not say that the different MPH formulations have different profiles of symptom response. I would say they have different time-action profiles. Small point, but best not to create the impression that the different formulations address different symptoms.

Response
We agree that the original wording may be misleading and have changed the text on page 8 as follows ‘The differing time–action profiles of symptom control provided by these long-acting MPH formulations may allow clinicians to target specific periods of the day that are particularly relevant for a patient, facilitating individualization of ADHD treatment.’

Comment 5) Pg 8. Some of the “non-response” to MPH is poor tolerability to the dose needed to achieve response. Most of the rest is partial response. Actual non-response is very rare.

Response
The text on page 8 has been modified to remove wording relating specifically to non-response and rephrased in line with the reviewer’s suggestion: ‘While MPH is effective in the majority of children in the short term, there is significant variation in individual response to treatment with a minority not achieving adequate symptom control and others unable to tolerate MPH due adverse effects and a minority of children do not respond to MPH therapy [14-16].’

Methods
Search methodology seems comprehensive, sensible and was clearly spelled out.

Response
We thank the reviewer for his comments. No action required.

Results.
Comment 1) The review of pharmacokinetic properties is comprehensive and quite valuable. It would be important to indicate how the relative differences in pK profiles affect how the different formulations should be used – since all cover the whole day but achieve peak drug levels at different times and also reach different maximum doses. Is this variability clinically meaningful or is this an academic point that is managed by the dose given?

Response
We believe that these differences are clinically meaningful (but obviously not for all patients) and have addressed these issues in the conclusion and clinical recommendations section. While flexibility in duration of symptom control is afforded by differing long-acting methylphenidate formulations, individual responses to any given product and dosing strategy
may vary substantially. As no one long-acting MPH preparation is clearly superior to another, information regarding ADHD symptoms, their severity and the way that they change across the day needs to be considered on an individual basis when selecting a formulation and optimizing therapy.

Comment 2) The short paragraph on adverse effects indicating comparability overall probably doesn’t convey enough information about whether AEs can be expected to be higher when blood level is also higher. I did find the information on comparison of the MPH patch to oral formulations to be instructive, as the delivery is so different there could theoretically be important clinical differences in how to use these drugs.

Response
As adverse events associated with methylphenidate have been comprehensively reviewed elsewhere (references 29 and 30 in the manuscript), we felt a detailed discussion regarding safety was unnecessary and outside the remit of this review. We have, however, expanded the Adverse events section on page 17, addressing the issues concerning the potential differences in AE profiles related to different PK profiles. As you will see, the evidence reported within the studies reviewed did not allow us to make detailed comments on actual differences.

Conclusions.
This section is generally fair and well done. Here are a few suggestions.

Comment 1) The recommendation to switch formulation if response to the chosen formulation is not adequate is not wrong, but it is also not particularly helpful. Since it is extremely unlikely that there will be no response at all to adequately dosed MPH, the issue of inadequate response would be more likely related to time-action effects and mismatch between delivery (pK) and demand. I would rather see a recommendation that the profile of response and need be considered in switching formulations. In addition, the point should probably be made (although outside the scope of data presented here) that switching to another stimulant or a non-stimulant will likely have a greater impact in cases of poor response beyond pK issues.

Response
We agree with the reviewer that improved response following switching to an alternative long-acting methylphenidate formulation is most likely owing to dose optimization and selection of a formulation with appropriately-timed symptom control and we have modified the conclusions and recommendations to strengthen this message.
With regard to the use of other stimulants and non-stimulants, we have now also briefly discussed this on page 35.

Comment 2) The call for more head to head studies with formulations other than Concerta is at once sensible and unnecessary. Given that none of the head to head studies produce new findings regarding response and tolerability that cannot be predicted by pK, I really wonder how many head to head studies are needed with what is essentially the same medication delivered in different ways (with the exception of d-MPH, which may be different).

Response
While studies have shown that the efficacy profile across the day of long-acting MPH is generally predicted by the formulation PK profile, we feel there would be benefit gained from further head-to-head efficacy studies, in particular laboratory school-style studies of alternative combinations of long-acting MPH formulations (as to date Concerta has been the main comparator) and in a variety of patient populations, both for the differentiation between formulations with similar MPH release profiles, and between those with different daily doses and immediate-release components. Further studies would support the development of clinical guidelines, inform the decisions of regulators and payers and ultimately support evidence-based guidance on treatment selection in daily practice. We have modified the text on pages 37–39 to further support the benefits of head-to-head studies and have incorporated the reviewer’s observation regarding the comparability of d,l-MPH and d-MPH formulations, as mentioned below.

Comment 3) The one medication that is most different is d-MPH. Whether d,l-MPH and d-MPH are comparable in effects or not (they should be since only d is active and l is quickly eliminated) has not been adequately investigated.

Response
The reviewer’s valuable observation has been incorporated into the text on page 38.

Reviewer: Liang-Jen Wang
Reviewer’s report:
The authors provide a systematic review of head-to-head studies with regarding to pharmacokinetics and efficacy of different long-acting methylphenidate (MPH) formulations. Overall, this paper is generally well-written and has several merits including originality of study design and important clinical topic. I have only discretionary revisions to suggest:

Comment 1) The authors suggest that “For patients achieving suboptimal effects with a long-acting MPH medication, switching to another MPH formulation should be considered” in
conclusions and clinical recommendations (Page 34, line 12). The conclusion might be mainly drawn from the evidence of the switching studies. However, I wonder how many switching studies conducted in a cross-over design. The results of open-label studies with single arm might be easily influenced by placebo effect or patients’ natural maturation.

Response

We appreciate the reviewer’s comment regarding placebo effect and maturation in open-label, single-arm studies. The two switching studies identified in the literature search were open-label and neither was conducted in a cross-over design. We have inserted a note regarding the open-label study design in the results (page 27) to inform the reader. The recommendation regarding switching was supported by results from the open-label switching and observational studies and also a randomized, double-blind, cross-over trial (Doepfner et al, 2011; reference 42 in the manuscript).

Comment 2)

In addition, because the health insurance systems are diverse over the world, different long-acting MPH formulations may not be concomitantly available for prescription in every country. The authors may want to provide a short description about the list of countries in which switching a long-acting MPH formulation to another is practical.

Response

The reviewer is correct in the observation that the availability of long-acting methylphenidate formulations will be an important factor in decision making when switching between formulations. We have included the countries/regions in which drugs are available in Table 1 and briefly noted the impact of availability on treatment choices on page 35.