Reviewer’s report

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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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.

Introduction. 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. 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. 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., metadata CD for Equasym. 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. 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.

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

Results. 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? 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.

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

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a
statistician.

Declaration of competing interests:

I consult with many pharmaceutical companies about ADHD medications. All are
publicly declared. None are so substantial as to preclude research. i receive
research funds from several companies as well. I would be happy to delineate
the various companies I consult to if that is required or considered to be helpful.