Reviewer's report

Title: Efficacy of Two Once-Daily Methylphenidate Formulations Compared Across Dose Levels at Different Times of the Day: Preliminary Indications from a Secondary Analysis of the COMACS Study Data

Version: 1 Date: 19 July 2004

Reviewer: Tobias Banaschewski

Reviewer's report:

General
Re:
Edmund J. S. Sonuga-Barke, James M. Swanson, David Coghill, Heleen H. DeCory and Simon J. Hatch BMC Psychiatry Efficacy of Two Once-Daily Methylphenidate Formulations Compared Across Dose Levels at Different Times of the Day: Preliminary Indications from a Secondary Analysis of the COMACS Study Data

When assessing the work, please consider the following points:

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

1-7.: yes.

The findings from the COMACS study (Swanson et al., 2004) suggest that differences in the PK profiles for MCD and CON at near-equal doses as measured by area under the plasma concentration time curve translate into statistically significantly different PD profiles on surrogate measures of behaviour and performance among children with ADHD in the laboratory school setting. For near-milligram equivalent daily doses, MCD provides greater symptom control in the morning, while CON provides greater control in the early evening.

The present paper presents a statistical cross-dose analysis of the efficacy of MCD and CON at different times of the day in order to directly test whether equivalent levels of morning symptom control could be obtained with lower daily doses of MCD than CON, respectively, whether lower daily doses of CON than MCD could have similar effects in the evening.

Results suggest that symptom control from 1.5 through 6.0 hours post-dose was as good with lower doses of MCD (20 and 40 mg) as with higher doses of CON (36 and 54 mg, respectively). Lower daily doses of CON (18 and 36 mg) and higher doses of MCD (40 and 60 mg, respectively) gave equivalent control at 7.5 and 12 hours with MCD giving better control from 1.5 through 6.0 hours post-dose.

Therefore, the authors concluded that different delivery profiles of MCD and CON can be exploited to limit total daily exposure to MPH.
It is clinically important to have empirical information available about the comparative benefits of differing doses of different formulations with different PK/PD profiles to guide the selection for use in a particular clinical situation. The paper is written theoretically stringent and methodologically sound. Relevant limitations are mentioned.

The authors reported in their first paper (Swanson et al., 2004) that

a) the interaction of dose x treatment was not significant, indicating that the pattern of treatment effects was consistent across each dose level.

b) clinical superiority at any point in time was achieved by the formulation with the highest expected plasma MPH concentration.

Given these findings, it seems logical that a lower dose of MCD, respectively CON would produce a weaker effect. However, I agree that these hypotheses should be tested statistically.

During the first 4.5 hours even 20mg MCD seem to have an equivalent efficacy as CON.

I must admit that the suggestions made by critics of Swanson et al., 2004, that “it has been suggested that it was inappropriate to base the selection of dosing levels for comparison on nearest mg-equivalent (as well as AUC-equivalent). For instance, it has been suggested that comparators could have been matched on the basis of the size of the initial bolus dose of the IR component rather than the total daily dose” are not convincing me.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

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Discretionary Revisions (which the author can choose to ignore)

1) The placebo superiority immediately after dosing should be explained in this paper, as well. In their first paper, the authors offered 2 speculations about possible mechanisms that could account for this difference, i.e., firstly, that shortly after dosing, the brain concentrations of MPH may have a preferential effect on presynaptic compared with postsynaptic dopamine receptors, resulting in the inhibition of dopamine release, and, secondly, that acute tolerance may result in a “rebound” such that behaviour and performance are worse in the morning before the single daily dose is administered.

2) Design: number of subjects in each condition should be mentioned.

3) Effect sizes of the differences at time points should be given. I agree that the reader might calculate those from the results presented in table 2.

4) For the statistical analysis, a weighted combined SKAMP score determined by PCA over all observation points was used. It might be helpful to state which SKAMP scores loaded to which degree on this score.

What next?: Accept after discretionary revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable
Statistical review: No

Declaration of competing interests: None