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

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Reviewer: John T Wilson

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Review of a manuscript that utilizes information from a prior study requires a priori comments on the original work (i.e., Swanson et. al., "A Comparison of Once-Daily Extended-Release Methylphenidate Formulations in Children with Attention-Deficit/Hyperactivity Disorder in the Laboratory School (The COMACS Study)", PEDIATRICS, 133,3, March 2004, E206-216).

Note that this study per force is subject to the same limitations as those for the study by Swanson et. al., 2004 (The COMACS Study). Careful reading of statements qualified appropriately for "predicted", "PD" vs clinical outcomes, and the "theoretical PK/PD model" is required in order to avoid over-interpretation of results.

In addition to concerns raised about patient assignment to dose groups, Sonuga-Barke et al raised an issue about nearest mg-equivalent dose selection as opposed to use of the size of the MPH formulation IR component. They also address concerns about subject selection unbalanced for disease severity, because placebo scores were higher in children assigned to the high MPH dose group. In an attempt to compensate for this, the outcome scores were adjusted for those from the placebo group. There remains, however, a concern that the optimum effective dose of MPH was not used in these children. Other considerations that may be more relevant to the high dose group include erroneous diagnosis of ADHD and disproportionate co-morbid conditions, compliance failure, or atypical PK profile.

The objective of the Sonuga-Barke study was to evaluate the total SKAMP scores from the Swanson study in regard to formulation, dose and time of day, i.e., a statistical cross-dose analysis. Effects of performance site, sequence of drug administration, and patients with missing data were not included in the analysis. The authors propose that delivery profiles of a MPH formulation can be used to select lower doses and target certain periods for optimum therapy of children with ADHD. As they emphasize, this requires a prospective study with random assignment of children to different dose levels of the two MPH formulations in question. We would add that plasma levels of MPH should be assessed and the appropriate PK/PD model developed from the population under study. Random assignment and plasma level data would substantiate (or not) concepts advocated by Swanson et. al. 2004 and by Sonuga-Barke et. al.

The Methods section of the paper is a synopsis of the description by Swanson et al 2004, and is subject to the study design limitations already discussed. (Extensive review of statistical concepts and programs requires attention of an expert statistician.)

Preliminary analysis was consistent with the findings of Swanson et. al. 2004 in regard to period-specific effects of MCD and CON. From Table 1, the MCD gives a higher amount of IR MPH at each dose strength than CON, whereas the dose strength of both formulations gives a similar amount of the ER component. From Figure 1, the respective comparisons for dose strengths of MCC and CON produced Total SKAMP Score effect differences for sessions as follows: Low to Mid showed MCD at 1.5 hr and CON at 12 hr; Mid to High showed CON at 7.5 and 12 hr.; Mid to Low showed MCD at 1.5 to 6.0 hr; and High to Mid showed MCD at 1.5 to 6.0 hr. (Greatest effect is noted for the formulation mentioned at sessions shown.)
The first paragraph of the discussion section presents two predictions, based on the different delivery systems of the two preparations giving different amounts of IR and ER at periods after dosing:

First, that MCD would provide greater control of ADHD symptoms in the morning, and
Second, that CON would provide greater control of ADHD symptoms in the afternoon.

The authors conclude that these predictions were only partially supported (p. 15, last line). Of note was that MCD 40 mg and CON 54 mg (each with 12 mg MPH IR) showed similar effect at 1.5 through 4.5 hr but also at 6.0 hr after dosing. MCD 20 mg (6 mg IR) gave early effects as compared to CON 36 mg (8 mg IR) (but with an expected greater effect from CON (28 mg ER vs 14 for MCD) at 12 hr). This presents a challenge to the concept advanced by Swanson et al 2004 that efficacy in ADHD children is related to plasma level of MPH and hence predicted from IR and ER components. Sonuga-Barke et al then hypothesize that non-drug-related factors may be involved (p. 16, first paragraph), such as dissolution characteristics important for bioavailability of MPH in each formulation. Overlapping release of IR and ER components could lead to unexpected amounts of MPH at periods after dosing. Apparently, as stated, dissolution studies support differences between MCD and CON for release of ER MPH. To further confound the issue, the authors suggest a dose (strength?) effect. If so, then this may weaken comparisons between dose groups. Greater efficacy for the mid and high dose CON (36 and 54 mg) at 7.5 hr and 7.5 and 12 hr respectively is deemed expected on the basis of PK profiles. This comment is difficult to interpret since no plasma levels were done, and since, according to Table 1, the amount of ER MPH is similar for CON and MCD. A prediction that appeared in Figure 1 was that low and mid doses of CON gave effects equivalent to mid and high doses of MCD at 12 hr post dose. Early period enhanced efficacy of MCD at these doses appears consistent with a higher IR MPH component for this formulation. The authors should again consult Figure 1 in the paper by Gonzales et al 2002 for the MPH plasma level profile from MCD and CON as such data impact bioavailability and time course release characteristics for the formulations.

A problem with descriptions throughout the paper is use of the term "PK" when dose or dissolution characteristics are the parameters in question. Plasma levels of MPH and a PK profile were not determined in these children. A lack of such data, it would seem, leads to difficulty with interpretation of unfulfilled predictions.

p. 17, paragraph 2 "Given design limitations it is possible that these effects are not "real" effects related to dose and treatment type but rather are related to differences between the types of children assigned to different dose levels."

Notable confounders mentioned by the authors include types of children in a given dose group, sensitivity to MPH dose independent of ADHD severity (such that sensitivity rather than cross-dose comparisons are being made), and frequency of dose administration as a basis for assignment to a dose group. Rebuttals to possible confounders are discussed.

It is important that care be exercised in extrapolation of adult data to children, application of theoretical PK/PD models, estimation of drug bioavailability without plasma level-time course profiles in the subject population, formulation dissolution characteristics or metabolic clearance that may be affected by dose, and for assumptions about response-concentration relationships in those with different severity of illness.

Much to their credit, the authors qualify and describe their findings as "...initial indication of the relative efficacy of different doses of CON and MCD at different points across the day...and should be treated with a certain degree of caution..."

We agree.

Reviewers:
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What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes