Reviewer's report

Title: A modelled economic evaluation comparing atomoxetine with methylphenidate in the treatment of children with attention-deficit/hyperactivity disorder in Spain

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Reviewer: Michael Schlander

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Peer Review Report

BMC Psychiatry - Hong et al., A modeled economic evaluation comparing atomoxetine...

Q1 Is the question posed by the authors well defined?
Yes. The question is well defined.

Q2. Are the methods appropriate and well described?
The Markov model was described previously (Cottrell et al., 2008) and seems an appropriate way to represent the clinical pathway of patients with ADHD.-

Q3. Are the data sound?
There appears to be an issue regarding the utility data used (reported by Secnik et al., 2005). The authors claim these were based on “a rigorously conducted utility evaluation study of ADHD-related health states” (manuscript p. 15). See below, major compulsory revisions.

Q4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
I have not found any obvious flaws in this respect. I consider the manuscript o.k. insofar.

Q5./Q6. Are the discussion and conclusions well balanced and adequately supported by data? / Are the limitations of the work clearly stated?
There are concerns re. Q5 and Q6, please see below.

Q7. Do the authors clearly acknowledge any work which they are building upon, both published and unpublished?
The study is largely similar to a UK study by Cottrell et al. (Value in Health, 2008), but this study is mentioned. The present report essentially extends the findings reported by Cottrell et al. (2008) to Spain. Parts of the present report are remarkably similar to the UK study quoted.

Q8. Do the title and abstract accurately convey what has been found?
Title is definitely o.k.; as to the abstract, see comments below as to utility weights used, which were a critical input to the study.

Q9. Is the writing acceptable?
Yes, it is.

In the following, I will focus on essential revision needs. A minor point relates to the omission of a note on the cost effectiveness of long acting medications for ADHD, which appeared in European Child + Adolescent Psychiatry in 2007. This not suggested inferiority of atomoxetine compared to stimulants given its higher cost and lower (or at best equal) symptomatic response rates, compared to methylphenidate. This discrepancy with the findings of the present study should be discussed by the authors.

Minor essential revisions
The cost effectiveness of a medication management strategy for ADHD in children and adolescents has been evaluated in a number of studies addressing the impact of coexisting conditions (e.g., Foster et al., 2007; and others), which were based on the major study in the field, the NIMH supported MTA Study. These findings might be discussed.

While the NICE ADHD assessment has been quoted to support the authors’ claim that there is no identifiable difference in effectiveness between atomoxetine and methylphenidate (p. 3), the critique that this assessment did not make full use of the available clinical evidence (see Schlander, Health Technology Assessments by NICE…, New York: Springer 2007). In fact, other analyses did report differences in favor of methylphenidate (Steinhoff, 2003; Faraone, 2003; Faraone et al., 2003, 2006; for a discussion, you may refer to Schlander, 2007, pp. 132f.).

Of note, however, all these studies (including the present one) are limited in scope due to their primary focus on symptomatic improvement. Therefore, the importance of functional improvement of patients (and outcomes beyond those mentioned) should be discussed in more depth.

Major compulsory revisions
The present study has been focused on symptomatic response rates, which were subsequently transformed into QALYs using utility weights for responders and nonresponders. It is not clear what evidence provides the basis for the assertion that “the nature of response with atomoxetine, which was reflected in the health state descriptors used in the utility valuation study, is preferred to that of stimulant treatments” (cf. Cottrell et al., 2008, p. 386). The authors should address this issue and, for the present manuscript to be accepted for publication, be able to persuade readers of the manuscript that the “rigorously conducted utility valuation study” – supported by the manufacturer of atomoxetine – did not fabricate the results needed for an economic evaluation showing acceptable cost effectiveness of atomoxetine.

Background: According to the NICE assessment (King et al., 2004, p. 240), “the
review ... highlighted some concerns about the validity of these estimates, [note added: referring to these utility estimates] particularly the fact that the utility of a non-responder without side effects differs between treatments. For example, the utility associated with non-response to atomoxetine, without side effects, is estimated to be 0.902, which compares to an estimated utility of 0.880 associated with non-response and no medication. A difference in utility of 0.022 is relatively large in this population, particularly between health states with identical characteristics. ... so the sensitivity analysis uses the utility of non-response associated with no medication.” Interestingly, the cited study (Secnik et al., 2005) also reported a higher utility (of 0.886) for atomoxetine “nonresponders” with side effects than for “responders” without medication (0.880; poster presentation by Secnik et al., 2004, at ISPOR meeting in Arlington, Virginia; cf. also NICE assessment report by King et al., 2004, p. 217). Since then a series of closely related papers (Matza et al., 2004, 2005; in addition to Secnik et al., 2005) has appeared in various journals, reporting details on the elicitation of those standard gamble scores. As it turns out, the description of health states (Secnik et al., 2004, 2005; cf. also NICE assessment report, appendix 10, pp. 359-366) for patients treated with stimulants with “no side effects” includes symptoms associated with insomnia, which has been listed as a “side effect” separately in the description of corresponding health states “with side effects” – which may amount to double-counting and is the only conceivable explanation for the twice as high differences in utility gains reported with nonstimulants (i.e., atomoxetine; difference, 0.06) compared to stimulants (i.e., methylphenidate immediate-release; difference, 0.02; or methylphenidate-extended-release, difference, 0.03). As mentioned earlier, this series of experiments was conducted under contract with the manufacturer of atomoxetine and should be interpreted with caution.

As to the present study, these observations appear highly relevant since (a) it is also sponsored by the manufacturer of atomoxetine and (b) it is heavily building on these data. These issues were also identified previously in the NICE monograph (Schlander, Springer, 2007, p. 61), and these concerns should be adequately addressed by the authors of the paper under consideration.

Prof. Dr. Michael Schlander
Heidelberg and Wiesbaden, October 19, 2008

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

Quality of written English: Acceptable

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

Declaration of competing interests:
See comments above. InnoVal-HC and/or some of its members received research and/or speaking support and/or provided consulting services to the NIMH, J&J, Pfizer, Shire, Novartis, and Lilly. Currently, however, there are no contractual relations in place with any of these parties.

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