Eur Child Adolesc Psychiatry (2016) 25:339–340
DOI 10.1007/s00787-016-0845-2

EDITORIAL

Is the evidence base of methylphenidate for children and adolescents with attention-deficit/hyperactivity disorder flawed?

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Published online: 28 March 2016

The increase in methylphenidate use in many European countries and many other parts of the world [1, 2, 4], has raised a considerable concern in society about the possible overtreatment of children with psychostimulants. European guidelines for best practice from the healthcare associations and authorities for the treatment of attention deficit hyperactivity disorder (ADHD) recommend that methylphenidate (which has a marketing authorization as part of a comprehensive treatment program for ADHD in children aged 6 years and above) should only be the first treatment choice in case of severe levels of symptoms and impairment associated with ADHD. Parent training is indicated if the child has ADHD with mild or moderate symptom severity and levels of impairment. Only if the response to parent training is insufficient and significant impairments remain should medical treatment be considered. It is unknown how well the current prescription practice of methylphenidate across Europe is in line with these guidelines, and why there has been such a rise in prescription rates.

A recently published Cochrane systematic review [3] has now added a new layer of doubt on the use of methylphenidate for children and adolescents with ADHD, by indicating the evidence base of methylphenidate to improve ADHD symptoms to be "of very low quality". The authors identified a total number of 185 randomized controlled studies of methylphenidate versus placebo or no treatment (38 parallel group trials involving more than 5000 participants; and 147 cross over trials with over 7000 participants) and assessed all 185 as being at high risk of bias.

We agree it is important to critically consider the role of potential bias due to vested interests in scientific reporting in general and in medication studies in particular. This should, however, be achieved by the empirical testing of whether bias has really distorted the analyses of data, reporting of results and drawing conclusions. The approach by Storebro et al. [3], is completely different and ends in a deadlock. They appear to introduce a new ideology: by definition reports that have been sponsored by industry and/or co-authored by experts from industry or experts with declaration of interests are untrustworthy.

Another main source of bias according to the authors was the fact that it may have been possible for people in the trials to know which treatment the children were taking based on the adverse events that occurred more frequently in children on active treatment compared to placebo. Thus, the authors stated in their plain language summary: "At the moment, the quality of the available evidence means that we cannot say for sure whether taking methylphenidate will improve the lives of children and adolescents with ADHD." And: "It was possible for people in the trials to know which treatment the children were taking." As a major implication for research the authors recommend comparisons with "nocebo tablets", designed to have similar adverse events as those associated with methylphenidate.

A quick PubMed search revealed the term nocebo in no more than 47 articles involving the clinical trials. However, none of these clinical trials used a nocebo tablet as comparator. Thus, when following the reasoning of Storebro and colleagues virtually the whole evidence base of medicine is of very low quality. But there is more to critically

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reflect upon. The main outcome measure in the studies was teacher-reported ADHD symptoms, while the most frequently reported adverse events were sleep problems and decreased appetite. Such non-serious adverse events are not typically discussed with the teachers. Why then was it "possible for people in the trials to know which treatment the children were taking"? Moreover, there was not a tremendous increase in the rates of adverse events in children on active medication, which was about a quarter more than in the placebo group. It is highly unlikely that this has in all cases led to deblinding. Furthermore, medicine knows many medications with much higher likelihoods of adverse events compared to placebos.

For an article with such strong conclusions, we were also disappointed to read a number of inaccuracies. Strangely, the Multimodal Treatment Study of ADHD was included in the meta-analyses, even though that study did not involve comparisons with placebo. Furthermore, in the abstract we read that all 185 studies had high risk of bias, whereas according to the results section, there were still 3 % of studies without such high risk. While this is indeed a very small subgroup, such inaccuracies do not add to a feeling of confidence towards the authors' analyses. A final indication of inaccurate reasoning involves the following quote from the article "the fact that the intervention effect of methylphenidate on ADHD symptoms did not differ significantly between the trials at low risk of bias compared with trials at high risk of bias may be taken as an indication that deblinding has occurred among former trials." This is an unexpected reasoning for at least two reasons. First, the article has stated that there was not a single study at low risk of bias. Why then can such a statement be made? Apart from that, a much more straightforward conclusion from the fact that the intervention effect of methylphenidate on ADHD symptoms did not differ significantly between the trials at low risk of bias compared with trials at high risk of bias would be to conclude that it is very unlikely that the identified bias has had a major influence on the results.

What to think of the authors' recommendations? We certainly do not endorse the use of nocebo tablets for future trials. A much more ethical and practical method to avoid the risk of deblinding is to involve independent raters of adverse events and of effectiveness. In our view, there are other priorities. We need well-conducted trials investigating the functional effects of methylphenidate on the long-term, e.g., on cognition and school performance. We need studies investigating the best sequence and/or combination with behavioral approaches. Finally the field would benefit from better analyzing the reasons for prescriptions. For example, why is there often undue pressure from school staff on parents to have stimulant medication prescribed to troublesome children? What has changed in the school system or society in general that teachers/parents feel less able to handle children with ADHD? How can we support parents and teachers better to deal with ADHD?

The authors' ideology should strictly speaking lead to a new situation where medication research is conducted by researchers funded independently from industry by public funding bodies like medical research councils. Dreams are the backbone of reality, as the novelist James Salter wrote, but it does not need long thinking to conclude that public funding bodies will never allocate the budgets needed to implement such a new policy.

Compliance with ethical standards

Conflict of interest Pieter J. Hoekstra has been a member of the advisory board of Shire. Jan K Buitelaar has been in the past 3 years a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly, Lundbeck, Shire, Roche, Medice, Novartis, and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, and royalties.

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