Antidepressant medications and other treatments of depressive disorders: a CINP Task Force report – a reply to Belmaker

Received 17 March 2008; Accepted 21 March 2008; First published online 18 April 2008

The letter from CINP President-Elect Professor R. H. Belmaker commenting on the CINP Antidepressant Task Force report (CINP Task Force, 2007) raises several crucial points that the CINP Antidepressant Task Force already addressed during the work on the report and the publication of the review. Some of the issues were resolved, others will continue to require attention in psychopharmacological research and in teaching, in pursuit of the major goal of improving recognition and treatment of depressive disorders.

(1) Professor Belmaker emphasizes that the CINP is an organization which should promote interactions between clinicians and scientists. He questions whether a review based primarily on a computer-based search in electronic databases truly reflects an unbiased approach. He is understandably concerned that most published trials are funded predominantly by pharmaceutical companies and that non-patented treatment alternatives are investigated often in smaller samples with inferior methodology which might have influenced the result of the Task Force review.

We regret this assertion because we were at great pains to adopt a proven methodology for minimizing bias. In our opinion the published review represents an excellent example for the promotion of interactions between psychopharmacologists working in research for universities or industrial companies and in medical care by the CINP. As Figure 1 indicates, during the process of the review a computer-based search of several databases was solely the basis for the production of the initial draft and a helpful tool for the writing of the second draft of the review. Several subsequent steps added expert opinions from all over the world. Thus, for example, we have included information about promising treatment options about natural remedies although the evidence about these treatments needs improvement (e.g. chapter 9.1.11 on herbal preparations, chapter 9.1.12.2.10 on Ω-3 polyunsaturated fatty acids). Information published in languages other than English about treatment options only available in specific parts of the world was also included because it was presented in worldwide consultative meetings. The available reports about those treatment options were, however, discussed and reviewed by the Task Force critically applying the usual scientific criteria.

(2) Professor Belmaker points out that placebo response in depression studies is high and even small treatment effects, which may be less relevant from a clinician’s point of view, may be highly statistically significant in large studies. He underlines the importance of recent studies such as the STAR*D trial investigating the treatment of depression in clinical situations closer to real life than the usual randomized controlled trials (RCTs). We agree that the translation of RCT results to clinical practice may be problematic. Nevertheless Professor Belmaker’s comments about the placebo response in depression studies take no account of our own extensive discussions in paragraph 4.4 ‘Limitations’ on page S12. We also underscored that statistical significance and clinical effectiveness may not be used synonymously and defined for clearer understanding the terms clinical effectiveness and efficacy in Box 6 on page S46. We also discussed the so-called ‘efficacy gap’ between outcomes in RCTs and the clinical practice which may be influenced by many factors including patient compliance. We also expressed concern that compliance in turn may be influenced by unbalanced media reporting on antidepressants (Wade, 2006). In addition the possibility of sponsorship bias and publication bias are evaluated and discussed in our review. Not all pharmaceutical companies have committed themselves to an open database policy of supplying information regarding all controlled, company-sponsored trials on their internet sites. In the review the CINP Antidepressant Task Force encourages this open database policy in addition to existing worldwide used databases for the registration of all clinical trials such as the EudraCT (http://eudract.emea.europa.eu/) or the Project Current Controlled Trials CCT (http://www.controlled-trials.com/) databases.

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Additional experts and co-authors (n=4)

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results, and we evaluated these results objectively using the clinical and scientific expertise of the members of the advisory board and the Task Force. We discussed in detail the issue Professor Belmaker highlights: that the population of patients included in RCTs differs significantly from the ‘natural’ population of the ‘real world’. To be aware of such a bias we attached importance to the initial results from the NIMH-sponsored STAR*D study as far as they were available during the time of the production of our review (for introduction see Menza, 2006). In addition, we extensively discussed the continuous increase in placebo response observed in RCTs during the last decades and the fact that low response rates to active drugs may be the result of the inclusion of chronically ill patients suffering often from depressive disorders resistant to a variety of pharmacological treatments.

We did not endorse a non-critical use of antidepressants, nor did we say that such a use should be promoted by the CINP. The review concludes that an informed use of antidepressant medication should be promoted for justifiable clinical indications. It follows from epidemiological data that the number of depressed patients needing but not receiving adequate treatment is high: an increased use and access to treatments for depression, including pharmacotherapeutic and psychotherapeutic approaches is therefore desirable. Appropriate education leading to a better recognition and treatment of depressive disorders is therefore important. Indeed, we believe a better education may also discourage family physicians from inappropriate prescribing of antidepressants when distress is more the issue than clinical depression.

(3) Professor Belmaker emphasizes that the CINP has a responsibility to countries and populations for whom expensive modern antidepressants and an adequate provision of psychiatric specialists may be beyond their available economic means. Does this change the science on which we evaluate our treatments? Does our review deny the usefulness of older medicines, in recognizing the relative advances, in terms of adverse effects, achieved by newer products. The answer to both questions is ‘no’, but again we agree that an exclusive electronic search and review of evidence does not allow clinically useful recommendations for clinicians in countries where economics precludes realizing such advice.

We nevertheless believe that our collection of evidence from databases together with the concentrated clinical experience of more than 200 worldwide accepted specialists in their field may even benefit countries where patent-protected expensive medicines, in recognizing the relative advances, beyond their available economic means. Does this change the science on which we evaluate our treatments? Does our review deny the usefulness of older medicines, in recognizing the relative advances, in terms of adverse effects, achieved by newer products. The answer to both questions is ‘no’, but again we agree that an exclusive electronic search and review of evidence does not allow clinically useful recommendations for clinicians in countries where economics precludes realizing such advice.

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We believe we are as aware of conflicts of interest and possible sponsorship bias, even in RCTs, as Professor Belmaker. We entirely concur that simply publishing disclosure statements may not resolve this problem completely. The CINP Task Force recognizes the inherent conflict of interest that pharmaceutical companies have, in pursuing profit and market share as opposed to unvarnished scientific truth. Within chapter 4.4 ‘Limitations’ on page S13 we therefore discussed the emerging attention on that problem and provided the readers with further references addressing such problems (e.g. Heres et al., 2006). In addition we mention that sponsorship bias may also influence publication bias, because publication of negative trials is usually not in the financial interest of the sponsor and may interfere with marketing strategies.

Professor Belmaker urges caution in the interpretation of results from RCTs. However, it would be irresponsible to promote the view that RCT methodology is rendered suspect or invalid by ‘conflict of interest’. Caution and scepticism in all things, but never nihilism. Moreover, the discourse of the popular press is not helpful in settling scientific questions. In the opinion of the CINP Antidepressant Task Force the introduction of RCTs and the publication of study results after an extensive peer-review process was a great step forward in psychopharmacology.

During our review process we used reports on RCTs registered in databases such as Medline and Cochrane Library as a scientific basis, but tried to correct and minimize the mentioned limitations by the process of worldwide scientific collaboration. In our opinion, extensive reviews including not only RCT results but also a broad clinical and scientific experience of designated experts in the field should support objectivity about information. The huge input the CINP Antidepressant Task Force received from the advisory board members was one part of this valuable support. The letter to which we are responding is another such piece of input.

Because not all information about failed and unpublished studies are available to date, the entire membership of the CINP Antidepressant Task Force agreed to promote and support an open database policy, encouraging pharmaceutical companies to supply information regarding all controlled, company-sponsored trials on their internet sites and in independent, freely accessible databases. Until this goal is achieved, critical reading of publications is essential, keeping in mind not only RCT results but also clinical experience. This may help to analyse published study results adequately.

Acknowledgements
None.

Statement of Interest

Thomas C. Baghai accepted paid speaking engagements in satellite symposia and acted as a consultant for AstraZeneca, Janssen-Cilag, Organon, Pfizer and Servier. Heinz Grunze receives research grants from Novartis, AstraZeneca, UCB Belgium and Pfizer. He occasionally supplies services as a consultant and/or paid speaker for AstraZeneca, Sanofi-Aventis, Desitin, Lilly, Janssen-Cilag, BMS and Pfizer. Guy M. Goodwin received grants from Sanofi-Aventis, Servier, and honoraria from AstraZeneca, BMS, Eisai, Lilly, Lundbeck, Pfizer, Sanofi-Aventis, Servier and Wyeth. He serves on the advisory boards of Lilly, Lundbeck, P1Vital, Sanofi-Aventis, Servier, Wyeth. He has no shares in pharmaceutical companies. He holds or has held research grants from Sanofi-Aventis, Lilly, Stanley MRI, the Bailey–Thomas Trust and the MRC (UK). Neither Brian E. Leonard nor any member of his family has financial interests in any pharmaceutical company. In the past, he has been an occasional lecturer at symposia sponsored by most of the international pharmaceutical companies that have contributed educational grants to the task force document. Before retiring from the chair of the Pharmacology Department, National University of Ireland, Galway in 1999, Brian E. Leonard received research grants from Eli Lilly, Pfizer, Pharmacia-Upjohn, Solvay-Duphar, Servier, Jouvenal Laboratories, GlaxoSmith-Kline and Organon. John C. Markowitz has been a consultant recently for Ono Pharmaceuticals; in the past he has received speaker’s honoraria and/or small consulting fees from Pfizer, BMS and Forest. Norman Sartorius acted as consultant and/or received honoraria for presentations at meetings and symposia organized by Eli Lilly, Janssen, Lundbeck, Pfizer, Servier and Wyeth.

References


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