Comment on: ‘Antidepressant medications and other treatments of depressive disorders: a CINP Task Force report based on a review of evidence’

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In 2004, CINP’s president, Brian Leonard, established a task force with the mandate ‘to provide mental health and other professionals with comprehensive and objective information about the different aspects of the use of antidepressants important in clinical practice’. The CINP Task Force presented its report (CINP Task Force, 2007) in an epidemiological framework with an emphasis on the need, individual and social, of using antidepressants on the widest possible scale. Then, it recommends the prescription of the newest and most expensive compounds on the basis of the ‘evidence’ reviewed in the report about their cost effectiveness compared to the older drugs. How could this happen?

(1) By the late 1980s single-centre isolated clinical studies were replaced by centrally coordinated clinical investigations. Many of these studies are designed for the purpose of registration by regulatory authorities and for supporting possible clinical advantages of new drugs. All the data from these investigations are proprietary, and all communication based on these studies, is controlled by the sponsoring pharmaceutical companies. Nevertheless, from the more than 1600 references reviewed only about 5% were published prior to the 1990s. By reviewing the literature from this period indiscriminately, the report endorses findings generated for marketing purposes and conclusions of ghost-written papers. By inserting comments from these papers which highlight the possible advantages of the newer and disadvantages of the older antidepressants the report reviews and presents the most comprehensive collection of promotional material to date for recommending the newest and most expensive patent-protected drugs.

(2) The task force dismisses all what has been learned in the first 20 years of pharmacotherapy with antidepressants and seizes every opportunity to discriminate against tricyclic antidepressants (TCAs), the dominant pharmacological treatment of that period. By treating TCAs – with the exception of Table 1 in the Introduction – as a pharmacologically homogeneous group of drugs, the report’s clinical recommendations are consistently skewed in the direction of newer and more expensive drugs. The report does not bring out that there are no cardiac conductance changes with doxepine, and in cases of overdose no fatal QTc time prolongation has been encountered with the drug. The report omits to mention that reboxetine, promoted since the 1990s as the first norepinephrine (noradrenaline) reuptake inhibitor, is pharmacologically homologous with desipramine, one of the first TCAs. It is also hidden in the text that venlafaxine, duloxetine and milnacipran, which are promoted as the first double reuptake inhibitors, are pharmacologically homologous with three of the old TCAs, i.e. dibenzepin, dothiepin and protriptyline.

(3) The serotonin reuptake inhibitors (SSRIs) are six of the 39 commonly used antidepressants reviewed in the report. They are not indicated in the treatment of severe depression. Yet, the task force recommends them as the first choice of treatment in depression. SSRIs, because of their pharmacodynamic properties, induce significantly more often psychomotor agitation, one of the recognized predictors of suicidality in bipolar depression, than TCAs. Nevertheless, after reviewing the extensive literature generated on this sensitive topic because of the vested interests involved, the task force concludes that findings about increased suicidal behaviour with antidepressants are ‘conflicting’, and ‘on the basis of the available evidence, any increased risk of suicide that antidepressants may produce in a subset (mostly adolescent) of depressed patients appears to be offset by the public health benefits of increased diagnosis and treatment of depression’. One wonders how sharing

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concerns about increased propensity for suicidality with SSRIs would interfere with diagnosing and treating people with depression, especially since SSRIs, as all antidepressants, are prescribed for patients who represent already an increased risk for suicide. But, be it as it may, the responsibility of physicians is to their patients, and even if the task force feels comfortable about possibly harming patients for alleged ‘public health benefits’, physicians do not have the right to do it.

(4) In our current era of evidence-based medicine, not only the approval of a drug for clinical use, but also the recommendations about how the drug should be used in treatment are derived from research-based evidence, expressed in a statistical probability figure. Nevertheless, the task force argues, that ‘evidence obtained in research is not the only evidence to consider in making treatment decisions’, and it has not disclosed the information on the research-based evidence used by regulatory agencies about the clinical indications of the 39 antidepressants discussed in the report. Neither has the task force revealed whether the statements and recommendations relevant to the use of antidepressants in the report are based on evidence (statistical), consensus or testimonials. Thus, the task force has not provided the necessary information to judge whether any of the statements and recommendations in the report meet the currently accepted ‘evidence’ by convention.

(5) The report culminates in a chapter on ‘Health economics: the cost of illness’ in which the task force tells physicians and regulators, that ‘we know’ on the basis of ‘economic evidence’ that treatment with SSRIs and with some of the newer, and even more expensive antidepressants are cost effective in comparison to treatment with TCAs. But, just as they did not reveal whether the 39 drugs they reviewed fulfilled minimal requirements of ‘efficacy’, and whether their clinical recommendations about the use of these drugs is based on evidence, consensus or testimonials, the task force did not disclose the assumptions used in cost effectiveness studies. Since most of the difference in cost effectiveness with antidepressants comes from an assumed increase in cost of illness by using drugs with anticholinergic and antihistaminic properties, it would have been prudent of the task force to focus attention on some of the older, inexpensive, bicyclic, tricyclic and tetracyclic antidepressants, such as amoxapine, dibenzepine, dosulepine, protriptyline and viloxazine, as they have neither anticholinergic nor antihistaminic side-effects. Treatment with any of these drugs would be far more cost effective than treatment with the expensive, still patent-protected, new drugs.

(6) By reinforcing the notion that depression-induced disability could be curbed by hunting down and treating all depressed patients with antidepressants, the task force distracts attention from the need of the field to develop a methodology for the identification of the treatment-responsive subpopulations to each drug in the broad diagnostic categories of major depressive disorder and depressive episode. The development of such a methodology would resolve the physician’s dilemma of prescribing an antidepressant with the knowledge that he/she might need to administer the drug to 2 in 3, or to 3 in 4 patients who can expect only to develop side-effects without any therapeutic benefit from it. Identifying the treatment-responsive subpopulations would reduce societal expense; break the impasse in improving the efficacy of treatment with antidepressants, and open the path for neuropsychopharmacological research to study the biology of depressions.

(7) The report of the task force does not provide the necessary basic knowledge and background information for mental health professionals to evaluate findings and recommendations about the use of antidepressants on their own, and for regulators to select cost-effective antidepressants for national drug formularies. By summarizing studies that were conducted to create a place in the market for each newly introduced antidepressant the task force has posted all the recommendations industrial marketing would have liked to post but was not allowed to do, and provided a guide for physicians to use and regulators to accept the newest and most expensive drugs.

(8) The report is of public concern because it was prepared in consultation with professionals serving as advisors to the task force who are able to influence the registration and inclusion of antidepressants in national drug formularies, and the teaching on the clinical use of antidepressants in the different countries. The report is already being translated into numerous languages and discussed in meetings organized with the help of these advisors around the world. Members of the task force participate in these meetings to urge the attendees with the authority of the CINP, a non-profit organization, to adopt the recommendations of the report. It is hoped that the task force is not used to set up a system that helps the international drug industry to aggressively market antidepressants.
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Statement of Interest

None.

Reference


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