

Do antidepressants really work?

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In the Jan. 17, 2008, issue of the *New England Journal of Medicine*, a "special article" described the selective publication of antidepressant trials and its influence on the apparent efficacy of such medications.¹ It was shown that 22 of the 74 studies entered in the Food and Drug Administration (FDA) data bank were not published, with all but 1 showing negative results. The general conclusion from these data on 12 antidepressant medications was that, from their diligent examination of the literature, clinicians would be led to make inappropriate prescribing decisions. This is because the effect size derived from the literature is larger than that calculated from all studies available to the FDA. The risk-benefit ratio of prescribing antidepressants is therefore higher than that estimated from the published literature. It was thus concluded that this "may not be in the best interests of their patients and, thus, the public health."

Is this breaking news? Certainly not, it is well known in this field that about one-half of such controlled trials come up with negative results. Some of the methodological reasons for such a high failure rate are explained below. Importantly, this information has been in the literature for quite some time.²

The first issue to emphasize is that the effect size, determined by subtracting the placebo effect from that of the antidepressant, does not adequately reflect real-world effectiveness. This is because the placebo effect is substantial in such 6–8 week trials. A major factor at play in this placebo response is attributable to the environment in which such research is conducted. When patients have suffered from depression for weeks or months, they have either been seeing a physician at long intervals or not at all. Suddenly, on entering a trial, they are generally seen weekly by a physician, a nurse or a research assistant, if not by all of the above. Patients can reach the research team by pager 24 hours daily, and a physician is always available to manage any problem arising. Thus the therapeutic effect of such conditions cannot be minimized. Such a placebo effect is, however, short-lasting. When placebo responders are maintained on placebo in the prolongation phase of these trials, and are seen at longer intervals,

many suffer a relapse. In contrast, when they switch to an antidepressant, they generally remain well.³

A second crucial issue is that risk-benefit ratios for using an antidepressant must not be estimated solely on the basis of the acute effects of these drugs. This is because depression is not an acute disorder. Depression must be treated for months or years, depending on the number of prior episodes and on several other factors. Therefore, the effectiveness of antidepressants in prolongation and maintenance studies must be factored in. In such studies, the therapeutic benefits of antidepressants are much more evident.⁴ To give an analogy, would anyone base his or her opinion on the effectiveness and benefits of a weight-loss program on an observation window of 6–8 weeks?

A third crucial factor for clinicians to consider when estimating the risk-benefit ratios of using antidepressants is to realize the impact of depression if it is not treated. Here familial, social and occupational functioning is of major importance. For instance, when mothers with depression achieve remission, their children will do significantly better in terms of no longer meeting criteria for DSM-IV diagnoses, compared with children whose index parent does not achieve remission.⁵ Absenteeism from work, as well as presenteeism (being at work but not performing adequately), represent critical problems in the workforce.⁶ Depression is associated with high suicide rates.⁷ Finally, depression makes most other medical comorbidities worse. To choose from numerous examples, there is a 5-fold increase in mortality when depression is present following a myocardial infarct.⁸

The *New England Journal of Medicine* article on selective publication of antidepressant drug trial results represents yet another paper that is implicitly teaching the public to fear antidepressant medications, when the major thrust in educating the public should really be directed toward fearing the illness. Such an alarming paper was preceded last year, in the same journal, by an article on the extremely rare occurrence of pulmonary hypertension in newborns whose mothers were taking antidepressants during pregnancy. This

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condition occurs in about 1/1000 newborns, in contrast to the 13% incidence of depression in mothers during pregnancy.⁹ Just a few years ago, antidepressants were purportedly linked to "suicidality" in children and adolescents, especially at the beginning of treatment. In this case, a new word (suicidality) was even invented to put under the same umbrella suicidal ideation and suicidal gestures, 2 clinical phenomena with different outcomes. In reality, there were no completed suicides in the 4400 children and adolescents who were analyzed retrospectively.¹⁰ Moreover, it was recognized early after the introduction of antidepressants, nearly 50 years ago, that treatment initiation represents a high-risk period for suicidal gestures after the patient's energy level improves but before the depressed mood begins to lift. Psychotherapy is also plagued with the same problem.¹¹

Antidepressants have been the subject of repeated attacks in recent years. It is certainly worthwhile to keep all medications under scrutiny, thereby raising awareness of potential problems with our pharmacopoeia. However, because of the way in which some papers are written, they may be seen as incendiary, thereby doing more harm than good to the public. When the news was broken concerning the *New England Journal of Medicine* publication, many prominent media outlets came to the conclusion, with a flavour of apparent fraud, that antidepressants may not really work. At the end of an interview on national television, the anchor told me that patients should stop their antidepressants, even after I had summarized the facts. My answer was that they should definitely not do so because antidepressants do work.

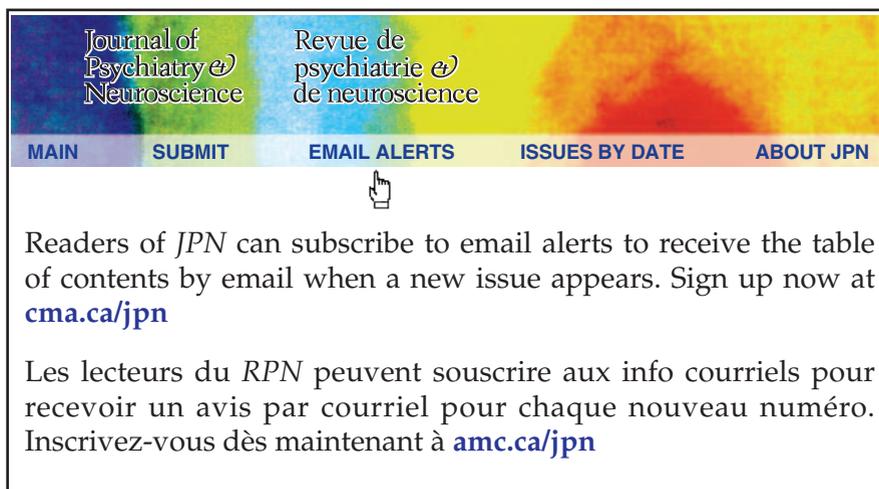
One can only wonder what will be the next known fact on antidepressants to be revisited in the near future and spun in an apparently ground-breaking negative fashion.

Competing interests: Dr. Blier serves as president of Medical Multimedia Inc. and is a contract employee of Steelbeach Productions, Forest Laboratories and Janssen Pharmaceuticals. He has received grant funding from Eli Lilly, Forest Laboratories, Janssen Pharmaceuticals, Lundbeck, Mitsubishi Pharma, Organon Pharmaceuticals, Wyeth-Ayerst and AstraZeneca. He acts as a consultant to Biovail, Eli Lilly, Forest Laboratories, Janssen Pharmaceuticals, Lundbeck, Organon

Pharmaceuticals, Wyeth-Ayerst, Sanofi-Aventis, Pfizer, Sepracor and Lundbeck, and serves on the speaker's bureaus of Cyberonics, Eli Lilly, Forest Laboratories, Janssen Pharmaceuticals, Lundbeck, Organon Pharmaceuticals and Wyeth-Ayerst.

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