SSRI treatment for under-18s

Let me see if I've got this straight. Industry bias in reporting the results of trials of selective serotonin reuptake inhibitors (SSRIs) is probable,[1] although an employee of a multinational drug company in another country doubts that this is so.[2] Another therapist (the author of a book reviewed in *CMAJ*) feels that mental illness has become far too commercialized (and the reviewer notes that, for pointing this out, the book's author has been personally maligned).[3] Data are lacking because they are not known (because of a globally inadequate system for reporting adverse drug reactions[4]), are not available (because they have not been published[5]) or cannot be discussed by physicians who have engaged in nondisclosure contracts.[6] SSRIs may be associated with an incidence of serious side effects (including withdrawals) of up to 25%, and the placebo response rate can be as high as 40% to 60%, although there may be a 70% response rate on some criteria of depression.[6] There is no evidentiary basis to prescribe or not prescribe SSRIs in patients under 18 years of age, and, either way, all of these uses are "off label" for patients in this age group. Furthermore, no clear leadership position is evident among child psychiatrists, almost all of whom are aligned with this controversy in some way.

As a personal standard, I try never to complain without offering some constructive suggestion. Having perused a selection of the currently available world literature on this topic, my impression is that SSRIs should be used with caution in this age group, and only as a last resort, after the failure of all other obvious psychosocial and environmental interventions, and with close attention to symptoms of mood instability (serious adverse behavioural and emotional reactions including agitation, irritability, behavioural disinhibition and suicidality).

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[Three of the authors respond:]

We wish to respond specifically to Mark Voysey's point that industry bias in reporting trial results is probable but that such bias has been refuted by an employee of a multinational drug company.

In our study, we found that industry-funded trials are associated with positive results in both medical and surgical randomized trials.[1] Hirsch,[2] an industry representative, argues against that finding. He states that Merck trial protocols undergo extensive scrutiny both internally and by external regulatory bodies and committees. Indeed, our review of trials found that drug trials achieved significantly higher mean quality scores than surgical trials (15.7 v. 13.4 out of a maximum of 21 points, $p < 0.01$). Companies such as Merck should be commended for their policy to publish the results of all "hypothesis-testing" clinical trials regardless of their outcomes. However, available evidence suggests that this policy is not universally applied by all drug companies. As reported in our study,[1] there is a large body of literature (1572 randomized trials) for which there is a greater than 2-fold odds of a positive study result in industry-sponsored trials compared with non-industry-sponsored trials (odds ratio 2.3). We do not believe that this is, as Hirsch characterizes it, a "relation … of modest degree." Ultimately, readers must critically examine all published trials with specific focus on the nature of industry involvement.

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[Dr. Herxheimer and Dr. Mintzes respond:]

Yes, we think that Mark Voysey has indeed got it straight, although we believe that it is not appropriate to prescribe SSRIs for children or adolescents even as a last resort. As outlined in our commentary,[1] there is just no convincing evidence that they work. Jureidini and associates[2] have pointed out that even among the minority of trials that have been published, authors consistently exaggerated benefits and downplayed serious risks. Overall, these authors concluded that trial results failed to support a benefit of sufficient magnitude to outweigh the risks.[2]

Voysey tries never to complain without offering some constructive suggestion. In a similar spirit, we suggest that the changes needed are systemic. Canada's parliamentary health committee has just released an excellent report,[3] calling for 3 key changes to drug regulation: better monitoring and public access to information on clinical trials, conditional drug approvals coupled with improved post-market surveillance and enforcement of Canada's law prohibiting direct-to-consumer ad-

vertising of prescription drugs. These changes are badly needed and would go a long way toward preventing similar future harm. Canada is of course not the only country in which drug regulation needs a radical overhaul: regulatory agencies in Europe and the United States also fail to adequately consider the public interest.[4]

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[Dr. Garland responds:]

Mark Voysey has summarized the challenge facing physicians who treat depressed children. Two additional and more detailed critiques of the published and unpublished evidence[1,2] are now available, and these reports underscore the fact that our evidence base has been distorted by selective publication and interpretation of data. However, as Voysey points out, a practical approach is required, and this may include judicious prescription of medication in individual cases, particularly in the presence of anxiety disorders, with appropriate monitoring.[3] However, evidence-based psychological treatments such as cognitive behavioural therapy and interpersonal therapy[4] need to be made more available.

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The best type of trial

James Wright[1] asks why we do not do more large simple randomized controlled trials (RCTs) in Canada. To support his point, Wright alludes to the differing results in observational studies on hormone replacement therapy and the results obtained in the Women's Health Initiative (WHI) clinical trial.[2] However, as pointed out in a recent article by Garbe and Suissa,[3] there were some serious methodological concerns with the WHI trial. In particular, the high rate of unblinding of gynecologists in the study introduced the potential for detection bias.

Clinical trials are important and have their place. However, we should not neglect the power of observational studies in determining drug outcomes. There is longstanding evidence that the results of careful observational research are very close to those obtained in clinical trials.[4] The power of a clinical trial is its ability to control for unknown confounders through randomization. But randomization is not a guarantee — it merely means that on average the unknown confounders will be balanced.

In an era of limited resources for health research, we must realize that not every study can be a clinical trial and that observational studies can provide accurate answers to questions much faster than RCTs. This can be important for conditions that require lengthy periods of follow-up. The key is to ask the right question and then use the appropriate type of study to answer it.

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James Wright[1] is mistaken in thinking that postmarketing conduct of a large simple RCT is the best way to resolve controversies associated with the introduction of new drugs. Such trials add more to the controversy than they resolve, as was the case with the ALLHAT study.[2]

Wright has missed fundamental deficiencies in megatrial methodology. The real-world RCT that he advocates would recruit a large and heterogeneous population, with few inclusion and exclusion criteria. The required simplicity is typically accomplished by not collecting clinical data that would allow analysis of important subgroups. The only outcome variable that can be better assessed in these heterogeneous conditions is eventual mortality, which may be low in some patient groups and of limited relevance in others.

Prior knowledge from both RCT