Antidepressants and adverse effects in young patients: uncovering the evidence

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Family physicians are repeatedly told that depression is underrecognized in patients of all ages and that lack of treatment can lead to serious harm. Selective serotonin reuptake inhibitors (SSRIs) and other, newer, antidepressants have been regarded as the treatment of choice in primary care, and inadequate reimbursement for nondrug alternatives such as cognitive and behavioural therapy has left little room for alternatives. It is understandable, then, that prescribers and parents in the United Kingdom were dismayed by a recent warning[1] from their national regulatory body (the Medicines and Healthcare products Regulatory Agency) that SSRIs are largely ineffective in the treatment of major depression in children and adolescents and can cause suicidal behaviour and self-harm. This warning is disturbing it itself, but it also leads to the question, Why did it take so long to discover this lack of benefit and potential for harm?

Part of the answer lies in the gap that exists between the quality of evidence needed to get a drug to market and the actual treatment needs of patients. A first episode of major depressive disorder typically lasts 7 to 9 months, and recurrence is common. However, the duration of most randomized controlled trials of antidepressants before marketing is only 6 to 8 weeks. One key measured outcome is a change in the patient's score on a physician-administered questionnaire such as the Hamilton Depression Rating Scale (HAM-D).[2] Such scales combine many different outcomes, and it is rarely clear from trial reports in exactly what ways patients felt better or worse. The HAM-D scale uses a single question to assess suicide risk, a measure that David Healy has roundly criticized as inadequate.[3] Further, in published studies, adverse drug reaction (ADR) reporting is often cursory.[4]

Premarket trials are often carried out in restricted patient populations that inadequately represent the users of a drug once it is on the market. For example, Zimmerman and colleagues found that 54% of a series of 293 adult patients diagnosed with major depression at a hospital outpatient psychiatric service had HAM-D scores below the threshold commonly used for trials of antidepressants.[5] Additionally, as Jane Garland describes in this issue (see page 489),[6] pharmaceutical companies are not required to disclose the results of negative trials (i.e., trials that show no efficacy or are inconclusive). Study data submitted by manufacturers to Health Canada during an approvals process are considered proprietary and thus are kept confidential unless a company chooses to publish or otherwise disclose them.[7] Also confidential are any rejected applications for drug approval in a specific indication or for the extension of an indication to another patient group, such as children. The secrecy that surrounds the drug approvals process means that physicians and their patients may be unaware that they are using a medication in a manner for which the evidence of effectiveness and safety is inadequate. Such policies value commercial interest above that of patients.

The postmarketing surveillance of safety and effectiveness also leaves much to be desired. Most countries, including Canada, rely primarily on voluntary reports of suspected ADRs in order to monitor drugs once they are on the market. The UK's Yellow Card system is regarded as one of the best systems for adverse reaction surveillance in the world, and has a much higher reporting rate than we achieve in Canada.[8] But even this system is inadequate. Medawar and Herxheimer evaluated 1555 anonymized Yellow Cards reporting withdrawal symptoms (1370), suicidal behaviour (91) or injury and poisoning (94) during paroxetine therapy between 1990 and 2002.[9] This study compared the quality of the information in the Yellow Card reports to that obtained directly from patients in 862 messages that had been sent to a Web site discussion forum from 2000 to 2002, and in 1374 emails sent to the BBC after a television documentary on paroxetine was aired. An analysis of these patient reports uncovered previously unrecognized patterns of experiences coinciding with dosage increases and withdrawal of therapy.[10]

Patient reports of ADRs are commonly dismissed as anecdotal or unscientific. However, the collective weight of the patient accounts of experiences with paroxetine therapy was profound. Reports from users and relatives — especially with respect to behavioural effects — communicated information that professional reporters can never be expected to provide. They were far richer, and described suicidality and withdrawal symptoms much more clearly and intelligibly than the Yellow Card reports. The analysis of over a decade's worth of Yellow Card reports suggests that

miscoding and flawed analyses by regulators led to an underestimation of the risk of suicidal behaviour during paroxetine therapy.[9] In some cases, depending on the word the reporter had used in submitting a Yellow Card, different terms were used to classify indistinguishable phenomena (e.g., "withdrawal," "discontinuation" and "dependence"). Most Yellow Cards lacked important information, such as the patient's history, the drug dosage and the outcome of the adverse reaction. Many reports of suicidal behaviour were very brief, and there was minimal evidence of follow-up. Indeed, scientists at the UK agency consider that its standard procedure for following up reports of serious adverse drug reactions[11] is in an important respect incomplete. Poor reporting and data processing have impeded the recognition of what seems to be a close relation between suicidal behaviour and changes in drug concentration (after dosage increase or decrease). But, quite apart from this, the data also suggest that SSRI dosages are far too high for some users.

Drug manufacturers had submitted 70% of the Yellow Card reports of "injury and poisoning" and 37% of the reports of suicidal behaviours on behalf of doctors. In contrast, companies submit only 17% of ADR reports in the UK overall. Reports sent by manufacturers tended to be euphemistic (e.g., by describing suicide attempts as "non-accidental overdose"). The value of the Yellow Card scheme is seriously limited by its emphasis on numbers rather than precision with words, by bureaucratic secrecy that obstructs wider access to anonymized data and by a lack of input from patients themselves.

The Yellow Card reports and the emails from patients included few reports about children and adolescents, but other accounts indicate that their reactions are qualitatively similar.[12] Thorough reviews are needed to clarify whether there are important differences between adults and younger patients. We must also look at conditions other than depression: SSRIs are widely used to treat, for example, obsessive–compulsive disorder, social phobia and generalized anxiety. The adverse effects in people with these problems seem likely to be the same as in depression — but we need the evidence.

The current voluntary system for reporting suspected ADRs is inadequate not only for SSRIs but for all medications. Neither the problems in the quality of Yellow Card reports for paroxetine, nor the value of patients' descriptions of their own experiences, are limited to this drug or class. Direct reporting of suspected adverse effects by patients is necessary in addition to reporting by physicians, pharmacists and nurses. In the UK, only health professionals may report suspected adverse drug reactions to the Medicines and Healthcare products Regulatory Agency. In Canada, reports from patients are accepted but not encouraged, and few people know of this option. A nonprofit organization, PharmaWatch, was launched in Canada in November 2003 with the aim of raising public awareness of drug safety and supporting consumer adverse drug reaction reporting.[13] Since no country has developed specific methods to handle patient reports, various pilot schemes need to be tried and evaluated.

The central recording, follow-up and analysis of ADR reports after a drug is marketed require a thorough overhaul. The focus should be on describing and understanding the reactions as clinical phenomena, their epidemiology and dose-relatedness, and on discovering the pharmacologic mechanisms. Other methods of adverse event monitoring using large databases, as suggested recently by Laupacis,[14] should be implemented and evaluated.

It is critical that anonymized reports be made available to the scientific and medical community: they come from the public and are needed for the public good. Publication should be encouraged, and the Internet offers excellent opportunities for doing so. Regulatory decisions based on adverse reaction data should be accompanied by publication of those data.

Regulatory requirements for evidence of efficacy should adequately reflect the key outcomes of importance to patients. The acceptance of broad exclusion criteria for pre-market phase III trials also needs rethinking. Most important, we need to broaden our understanding of informed consent in clinical trials. Can a patient be a truly informed participant in a trial if he or she is barred from knowing its outcome? All trial participants — and the broader public — should have access to the results of clinical trials.

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Facing the evidence: antidepressant treatment in children and adolescents

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Depression in childhood and adolescence is a challenging problem for those affected, their parents and their physicians. Before reaching the age of 18, about 1 in 5 young people will experience an episode of major depressive disorder, an illness that is characterized by a high recurrence rate, persistent psychosocial impairment and increased risk of suicide. Disappointed by the ineffectiveness and potential toxicity of tricyclic antidepressants,[1] physicians welcomed practice guidelines in the late 1990s that suggested the newer selective serotonin reuptake inhibitors (SSRIs) were effective and better tolerated.[2] The prescribing rate for antidepressants, particularly SSRIs, in young people has increased steadily in the past decade.[3]

However, 2003 brought surprises for both researchers and treating physicians. In light of the results of several large randomized controlled trials, regulatory agencies in the United Kingdom, the United States and Canada declared that paroxetine was contraindicated in the treatment of major depressive disorder in patients under 18 years of age. These trials had shown paroxetine to be ineffective and to be associated with double the rate of suicidality and aggression compared to placebo.[4] Next, 3 trials of venlafaxine therapy for pediatric depression found this SSRI also to be ineffective, and to be associated with double the rate of suicidality and hostility compared to placebo.[5] A general advisory was then issued regarding the increased risk of suicide in pediatric use of *all* SSRIs.[6,7] These developments not only raise new concerns about the presumed effectiveness and safety of SSRIs for young people, but also pose disturbing questions about publication bias and the questionable interpretation of research data on the treatment of childhood depression.

It is important to recognize that the SSRI therapy for young people with depression is characterized by high placebo response rates.[1] Twelve small double-blinded controlled studies published by the mid-1990s demonstrated no effect of tricyclic antidepressants or fluoxetine compared to placebo in childhood and adolescent depression, and a placebo response rate of 40%–60%. Pharmaceutical companies, perhaps encouraged by patent extension legislation in the late 1990s, undertook larger trials with the hope that greater statistical power, careful patient selection, higher doses and a longer duration of treatment (8–10 weeks) would yield more favourable results. The few trials published to date show minimal effects that, from a clinical standpoint, are trivial. For example, the recent sertraline study[8] involving almost 400 patients from 2 pooled trials demonstrated borderline statistical significance on selected measures of improvement, but these did not include remission, the most clinically important outcome. Sixty-nine percent of patients improved on medication, versus 59% on placebo. Essentially, only 1 in 10 patients receiving sertraline improved, a result described in the report as "statistically and clinically significant" when it is almost certainly clinically meaningless. The term "statistical power" implies that a large trial is inherently better than a smaller one. However, a clinically significant response should be evident in a small trial; a large trial is needed only to detect very small effects, which may or may not be clinically meaningful.

Fluoxetine is the only antidepressant that has received