Research

Health advisories: when good intentions go bad

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∞ See related research article page 1005

Health advisories for drug therapies are issued by regulatory bodies such as Health Canada with the best of intentions: to protect the public. Such advisories are backed by teams of internationally renowned experts convened by these regulatory bodies to review and interpret the available scientific evidence related to drug safety and effectiveness.

Variability in the interpretation of available scientific evidence can lead to different actions by different regulatory bodies. In 2003, the Department of Public Health in the United Kingdom advised against antidepressant use in children over concerns of increased risk of suicidality, whereas in the following year, Health Canada and the US Food and Drug Administration issued warnings aimed at greater vigilance for children under 18 receiving antidepressants.[1] The Food and Drug Administration's meta-analysis of pediatric studies examined clinical trial data for 4582 children and adolescents in 24 antidepressant trials of 4–16 weeks' duration and demonstrated an increased risk of drug-induced suicidal behaviour when compared with placebo (relative risk 1.95, 95% confidence interval 1.28–2.98).[2] These results suggest that 1%–3% of children given an antidepressant could be at risk of drug-induced suicidality. This disturbing finding was supported by an observational study by Olfson and colleagues,[3] who reported a nearly 16-fold increase in suicide deaths associated with antidepressant use among children and adolescents. On the basis of these data, one would expect that a reduction in antidepressant use should result in a decrease in suicide rates among children and adolescents.

In this issue of *CMAJ*, Katz and associates[4] report on the impact of Health Canada's warning on the rates of antidepressant prescription, ambulatory visits because of depression and completed suicides among more than 265 000 children (age 5–11), adolescents (age 12–17) and young adults (age 19–24) in the province of Manitoba annually from 1995 to 2006. Using comprehensive population-based administrative databases and a longitudinal study design, the authors report a decrease of 14% in antidepressant use among children and adolescents following the Health Canada advisory. However, they also report a 10% drop in the rate of ambulatory visits because of depression and a 25% increase in the rate of completed suicide in this group. Interestingly, the rate of attempted suicide did not change among children and adolescents. In contrast, although similar decreases in the rates of antidepressant use and ambulatory visits because of depression were observed among young adults, a change in the rate of completed suicide was not observed, which is consistent with data for adults in clinical trials.[2] The findings from the study by Katz and associates[4] corroborate those from a recent study by Gibbons and colleagues,[5] who also reported reductions in antidepressant use and increases in suicide rates in response to regulatory warnings among children and adolescents in the United States and the Netherlands. Other regions, however, have reported very limited impact of the health advisories on antidepressant prescribing patterns.[6]

Key points

- Health advisories are issued to protect the public, but regulatory bodies face the dilemma of balancing this objective with uncertainty in the underlying evidence.
- Scientific uncertainty associated with health advisories creates a risk of unintended consequences.
- Studies of antidepressant use in children and adolescents have suggested an increased risk of drug-induced suicidality. However, other studies have shown that, after regulatory warnings about this risk, decreased antidepressant use was associated with increased suicide rates.
- Both types of studies have limitations that create uncertainty regarding suicidality estimates.
- Health advisories should strive for more balance by presenting warnings in the context of prior evidence, balancing risks and benefits of therapy, and being explicit about residual uncertainty.

So what are we to make of these 2 bodies of ostensibly contradictory data? One suggests antidepressant use increases the risk of suicidality among children and adolescents, and the other suggests decreased use of antidepressants results in an increased risk of suicide. How do we best communicate this information to patients and health care providers?

Although the US Food and Drug Administration's meta-analysis of pediatric data demonstrated an increased risk of suicidality, it is important to note that patients who reported suicidal ideation or suicidal behaviour were excluded from the trials. Only a surrogate measure of suicidality rather than completed suicides was assessed, since no such events were reported in these trials. The latter point is particularly important, since the apparent increased risk of drug-induced suicidality may actually represent an increased likelihood of suicidality events being reported by patients receiving treatment rather than an increased rate of the events themselves.[2] Patients receiving antidepressant therapy may have been more likely than

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those given a placebo to have reported an adverse event, to have been approached for further evaluation and to verbalize and communicate their experiences as a result of effective treatment. Further, there was a lack of concordance in establishing risk of suicidality associated with antidepressant therapy: unexpectedly, there was an association when suicidality was reported as an adverse event outcome but not when it was reported as a suicide item on the depression rating scales that were systematically collected. These factors raise serious concerns about extrapolating the findings of the meta-analysis to infer an increased risk of completed suicide associated with antidepressants among children and adolescents.

Katz and colleagues' use of a large, comprehensive administrative database and longitudinal study design minimized the selection bias that often plagues most traditionally designed observational studies. However, as the authors note, their study was limited to a short duration of less than 2 years following the health advisory. Since the numbers of suicide events were low, even in this very large study, a longer duration of follow-up would be required to provide sufficient temporal stability to allow meaningful conclusions. The extent and consequences of abrupt withdrawal of antidepressant therapy following the health advisory rather than appropriately tapered discontinuation of these drugs are unknown. Interestingly, the authors observed no significant changes in the rates of hospital admission because of depression or suicide attempts among children and adolescents. Further, although the authors reported that the rate of ambulatory visits associated with depression decreased significantly following the warning, this outcome is difficult to interpret in the absence of data on overall rates of physician visits.

Equally important are the data related to the benefits of antidepressants. The evidence generally indicates modest to moderate benefits of antidepressants over placebo in treating major depressive disorder, obsessive compulsive disorder and other anxiety disorders in pediatric patients.[7] However, concerns of selective publication of positive trials that could lead to a biased impression of drug effectiveness have been raised.[8] In addition, the observed benefits of antidepressants are often criticized to be driven by a high placebo response,[9] and non-drug interventions such as cognitive behavioural therapy may be equally effective over the longer term.[10] Patient preference, however, must be considered in the treatment process.

Communicating the available evidence and the uncertainty surrounding it to patients and physicians is particularly challenging. The need for comprehensive information by patients[11] must be balanced by the ability to process complex information ingrained with uncertainty. Although health advisories provide focused and simple messages on a particular issue, they often lack a balanced presentation of the risks and benefits, and the level of underlying uncertainty for each.[12] The implications of these advisories can be quite substantial, as demonstrated by Katz and colleagues, for patients who may be adversely but unintentionally affected, for health care providers who care for these patients, and for the pharmaceutical industry and the people they employ, who have much to lose financially. More balanced advisories — in which new health care information would be placed in the context of the larger body of existing evidence on risks and benefits, and the underlying uncertainty surrounding the evidence — could provide a better basis for making important health care decisions that affect our well-being.

Competing interests: Muhammad Mamdani was employed by Pfizer Inc. from Jan. 1, 2006, to Apr. 7, 2007, after which he was a paid consultant to Pfizer until October 2007.

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