Key Opinion Leaders and Paediatric Antidepressant Overprescribing

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The lingering controversy about the usefulness and safety of antidepressants for children and adolescents is likely to leave clinicians in a state of confusion. Some papers report that there is little evidence for efficacy and raise concerns about harm\cite{1–3}; others state that antidepressants are not only safe and effective, but also prevent suicides\cite{4–7}. This journal has previously noted the influence on decision-making of irrational habits and misplaced trust in data submitted by the pharmaceutical industry\cite{8, 9}. In this editorial we address the manipulation of outcomes that result from academics’ alliance with industry. We explain how industry and key opinion leaders have distorted the clinician’s perception of the safety and usefulness of antidepressants for the treatment of depression in children and adolescents through publication bias, poor methodology, and selective reporting.

**Publication Bias**

Whittington et al.\cite{1} gained worldwide attention when they published data made available through the UK Committee on Safety of Medicines that allowed them access to unpublished as well as published studies of antidepressants for the treatment of depression in children. They found that whilst published results for a number of antidepressants suggested ‘equivocal or weak positive risk-benefit profiles’ the addition of unpublished data indicated that risk outweighed benefit\cite{1}. This is in keeping with the more extensive analysis of antidepressant trials in all age groups by Turner et al.\cite{10} that showed how selective publication inflated the apparent effect size of antidepressants by 32%. This was a consequence of the fact that all but 1 of 38 positive studies were published whereas only 14 of 36 negative studies were published (11 of those 14 were published in a way that conveyed a positive outcome).

**Poor Methodology**

Perhaps the most influential efficacy study of antidepressants in children has been the TADS study\cite{11–13}. The main methodological criticism of the TADS study is that it included an unblinded comparison between cognitive behavioural therapy (CBT) alone and fluoxetine plus CBT. This was carried out in parallel to a double-blind comparison between fluoxetine and placebo. The lack of patient blinding for medication status and placebo control for one half of the study is likely to have exaggerated the benefit seen in the fluoxetine plus CBT group who knew that they were not receiving placebo. The decision not to include a placebo in the CBT group was based on the belief that it was ‘both too expensive and too artificial to have clinical relevance’\cite{14}. This, however, is not a plausible explanation for why the CBT-only group could not have been converted into a CBT plus placebo group. In any case, the lack of placebo control for half the patients means that comparing results between parts of the trial, with and without a placebo control, is not valid. Yet
throughout the report of the study, comparisons are made or implied between these groups.

Gibbons et al. [7] provide another example of poor methodology when they examine the relationship between reduced antidepressant prescribing and increased suicide amongst youth by simplistically comparing suicide figures with the previous year rather than examining the change over several years without acknowledging the limitations of such comparisons. Similarly, they do not provide a denominator for their suicide figures; that is, they take no account of change in populations. Finally, like other ecological studies, they commit the ecological fallacy, i.e., a strong association between two factors in aggregate data is taken to be evidence of a causal link at the individual level. As the smoking-lung cancer case shows, ecological studies can be helpful when they have dramatic and well-replicated findings. Such is not the case with antidepressants. Some studies show a correlation between increased prescribing and decreased suicide [15–17]; others show the opposite [18, 19].

Selective Reporting

The antidepressant literature is undermined by data that is withheld or misrepresented, or by conclusions that are unjustified by the data.

Withholding Data

In 2001, Keller et al. [20] published a report of GlaxoSmithKline’s study 329 of paroxetine in adolescents that they claim showed that ‘paroxetine is generally well tolerated and effective for major depression in adolescents’. Yet we described how, when the study blind was broken, no significant difference between paroxetine and placebo was found on the 8 prespecified outcome measures [21]. The authors omitted from their report several outcome measures specified in the study protocol, replacing them with positive outcome measures, some of which were added after the blind was broken. Keller et al. also omitted details about adverse effects including suicide attempts. GSK celebrated study 329 as a ‘‘cutting-edge’’ landmark study’ that demonstrated ‘REMARKABLE efficacy and safety’ to sales representatives and it continued to spin paroxetine as superior to placebo in letters to health care professionals up to 2002 [22]. Our description of the manipulation of data [21] was only possible because we had access via litigation to protocols and other internal accompanying documents that outlined all of the measures and analyses conducted. Whether this was an isolated case, or whether the suppression of data unsupportive of the authors’ position is widespread, remains unknown.

Misrepresenting Data

Keller et al. [20] also significantly misrepresented data by claiming a positive response on a primary outcome measure that in fact proved negative, a misrepresentation that was facilitated by the paper being ghostwritten [23]. Wagner et al. [24] merged two studies into one in order to be able to report that a clinically trivial advantage for sertraline over placebo was statistically significant. More recently Gibbons et al. [7, p. 1357] concluded that decreases in prescriptions ‘were associated with increases in suicide rates in children and adolescents’, based on a 22% decrease in prescriptions after warnings were issued by the US Food and Drug Administration and the 14% increase in US youth suicide rates between 2003 and 2004. However, careful inspection of the data reported by Gibbons et al. shows that in the year in which suicide rates rose sharply, there was no significant drop in selective serotonin reuptake inhibitor prescribing, which only decreased the following year, when there was no increase in suicide. Both the figures and the discussion in the Gibbons paper give the impression that a clear association (if not causal relationship) has been established. In response to criticisms of his paper, Gibbons [25] did not comment on the apparent misrepresentation of US data, but introduced another data set that showed that US prescribing had increased early in 2004, then declined later in the year, for no net change, and argued that his Dutch data anyway showed the relationship he claimed. These responses have been disputed [26].

Unjustified Conclusions

A wide range of papers show a discrepancy between data reported and the conclusions drawn, whereby outcomes, especially in the abstract, are given a positive spin. Possible explanations for this phenomenon include a preexisting belief that antidepressants work well causing an unwitting bias in interpreting data, putting a positive spin on ambiguous results out of a belief that reassuring people about the safety and efficacy of antidepressants is a positive thing, and deliberate misrepresentation.

A common strategy is to downplay the failure on primary outcomes by emphasizing success elsewhere. Pador [27] has drawn the insightful analogy that this process is ‘akin to shooting an arrow and having it land on a wall and then drawing a target around it’. For example, the follow-up of the TADS study showed that any advantage to
sures showed benefit on protocol-defined outcome measures of the 20 trials on antidepressants in children and adolescents that compared response to drugs (50% to placebo). But no more than one of the 20 trials on antidepressants in children and adolescents showed benefit on protocol-defined outcome measures [29]. Similarly, when Bridge reports on harms from antidepressants, suicidality is the only harm considered, with no mention of other serious common adverse effects, manic switch or withdrawal effects [30–32]. And in weighing benefits against harms, the authors consider responder status (for which subjects only had to improve a few points more than in the placebo group) and suicidal ideation/suicide attempts as opposite but equal. Since there were more of the former than the latter, they conclude there is more benefit than harm, without considering that the harm of making one subject suicidal might outweigh the marginal benefit to several subjects.

Other manipulations of trial design favouring study medication have been documented in the literature include conducting a trial of study drug against weak competitor drugs, fixing too low or too high a dose of a competitor drug, conducting subgroup analyses and selecting for publication only those that are favourable, miscoding serious adverse events to hide suicide-related events, and excluding either placebo responders or active non-responders during the run-in phase thereby inflating response rates [33, 34]. We found direct evidence of several of these manipulations in our analysis of study 329 [21].

Another subtle misrepresentation is to ignore or downplay factors that may disqualify conclusions. In their study of suicide and antidepressant prescribing amongst adolescents in Manitoba, Katz et al. [35] claimed: ‘The rate of completed suicide among children and adolescents increased significantly after the Health Canada warning was issued (RR 1.25, 95% CI 1.08–1.44; annual rate per 1,000 = 0.04 before and 0.15 after the warning).’ This claim is based on comparing suicide rates up to the end of 2003 with those from the beginning of 2004. The fact that the sentinel event occurred nearly halfway through the 2004 calendar year is ignored. Similarly, in pressuring the case for the life-saving qualities of antidepressants, Katz et al. ignore the implications of 74–85% of Manitoban adolescents who commit suicide being aboriginal. It is unlikely that suicidal behaviour, utilization of Mental Health services or antidepressant prescribing are comparable in aboriginal and non-aboriginal populations, meaning that other factors are more likely to have changed suicide figures in the aboriginal population.

Misleading Influence of Key Opinion Leaders

With the help of public relations agencies, key opinion leaders have issued media statements to reassure prescribers about the benefit of antidepressants and the dangers of underprescribing [36]. While some psychiatrists have expressed reservations about RCTs in antidepressant research for some time, most antidepressant proponents were silent on the shortcomings of these trials for as long as publication bias and selective reporting had allowed a positive impression of their outcomes. Now that research evidence no longer suits their argument, advocates are dismissive of the usefulness of RCTs. Nutt and Malizia [37] are typical in raising doubts about the usefulness of ‘short trials in a recurring and relapsing condition’.

Where shall we place the blame for this deplorable state of affairs? Our answer is unequivocal. But are journal editors equally accountable for misrepresentation of data? The publication of the study by Gibbons et al. distorting the correlation between suicide data and antidepressant prescribing is a major editorial error, and it is hard to see how the misrepresentations in the paper by Keller et al. could have passed editorial scrutiny. There is also a significant concern with editors’ tendency to allow lesser transgressions of balance (for example, the Katz paper cited above) to pass into print. This disturbing trend in the medical literature points to a bias in favour of valuable commercial content as opposed to tough-minded critical analysis [38–40].

Pharmaceutical Marketing Strategy

Gaining control of the paediatric and adolescent depression market has been a clear objective of the pharmaceutical industry at least since the 1990s [41]. Companies were confident that they would have their licenses from regulatory authorities by 2000, but with the failure to gain the indications anticipated (except fluoxetine for major depressive disorders in the US and UK), a burgeoning off-label prescribing was achieved with the help of academics. Key opinion leaders in child psychiatry, who
have benefited greatly from industry support and appear not to have disclosed all conflicts of interest, have been active in delivering the message for the companies and in developing programmes designed to capture and increase the paediatric and adolescent antidepressant market [21, 42]. Yet pervasive conflicts of interest have been noted in connection with the psychiatrists who have pioneered the use of antidepressants in children and created new programmes of diagnosis such as ‘Teen Screen’ [43]. While a scant few voices have attempted to inform prescribers and the general public about the misrepresentation of the paediatric antidepressant data and the general lack of data on the long-term effects of these drugs on developing brains, such complaints have been virtually drowned out by the mainstream of marketing and drug propaganda [44]. The imperatives of marketing have overruled scientific authority. In addition, it has been questioned whether the very notion of paediatric bipolar disorder is an industry creation aided by corporate psychiatry [41]. In the United States, for example, a controversial 40-fold increase from 1994 to 2003 in the diagnosis of paediatric bipolar disorder has been attributed to the activities of researchers engaged in small-scale studies funded by industry [45]. The overdiagnosis and overprescription of antidepressants in children have followed the pattern in the creation of a depression epidemic largely undetected by the medical profession [46]. The end result, however, shows a consensus manufactured against the data – an embarrassment in an age allegedly devoted to evidence-based medicine.

Antidepressants have not been demonstrated to be safe and effective for the treatment of depression in children or adolescents. There is, however, good evidence that they do harm especially in connection with an increase in suicidal behaviour and ideation in younger patients [2]. Contrary to the overly optimistic reports cited above, they have not been shown to save lives. We cannot be confident about which patients, if any, should receive antidepressants, but we can be confident that many people who are prescribed antidepressants should not be. These conclusions are at odds with the clinical experience of many psychiatrists, perhaps explaining why authors, journals, and key opinion leaders have spun the data in a favourable way, rather than facing up to their disappointing implications.

In closing we address one caveat: while we argue that key opinion leaders have significantly compromised their ethical obligations by their extensive entanglements with commercial objectives of the companies, we are well aware that our own entanglements with litigation could result in the same charge. None of us appear to be without some industry connection. The question is whether such arrangements protect the integrity of science or create bias in favour of the company’s profit motive. We leave it to the reader to decide whether we are among the former or the latter.

Conflict of Interest

Jon N. Jureidini is chair of Healthy Skepticism, an international non-profit organization with a main aim of countering misleading drug promotion and was engaged by Baum, Hedlund, Aristei & Goldman law firm of Los Angeles, Calif. to provide expert opinion. Leemon B. McHenry is research consultant for Baum, Hedlund, Aristei & Goldman.

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