

## The contribution of pharmacoepidemiology to the antidepressant-suicidality debate in children and adolescents

JEFFREY A. BRIDGE<sup>1</sup> & DAVID A. AXELSON<sup>2</sup>

<sup>1</sup>The Research Institute at Nationwide Children's Hospital and Department of Pediatrics, The Ohio State University, Columbus, OH and <sup>2</sup>Western Psychiatric Institute and Clinic and Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

### Abstract

A number of concerns have recently been raised about whether or not antidepressant medications are associated with suicidal thoughts and behaviour in children and adolescents. These concerns are based largely on results of meta-analyses of randomized, controlled trials (RCTs). Controversy exists about generalizing evidence from short-term RCTs, designed primarily to test efficacy outcomes, to routine practice settings. Pharmacoepidemiological studies complement RCTs by using observational methods to examine safety and effectiveness of medications in the general population. This article reviews the contribution of pharmacoepidemiology to the controversy surrounding suicide risk in children and adolescents taking antidepressants, noting how variations in study design and adjustment for potential confounding factors influence outcome.

### Introduction

On 15 October 2004, the US Food and Drug Administration (FDA) mandated that a boxed warning be put on the labels of all antidepressants indicating an increased risk of suicidal thoughts and behaviour in patients younger than 18 years taking these medications (US Food and Drug Administration, 2004). On 2 May 2007, the FDA broadened the warning to include young adults ages 18 to 24 years (US Food and Drug Administration, 2007). These regulatory actions were based largely on results of meta-analyses of short-term RCTs demonstrating a higher risk of adverse event reports of suicidal ideation and/or suicide attempt during the trials in patients younger than 25 years (Hammad, Laughren, & Racoosin, 2006; US Food and Drug Administration, 2006). FDA analyses revealed a 2-fold (4% vs. 2%) increased risk of reported adverse events of suicidal ideation/suicide attempts in children and adolescents treated with antidepressants. In contrast, an analysis of 27 clinical trials found the benefits of antidepressants to outweigh the small risk (0.7% absolute risk increase) of suicidal thoughts and attempts for pediatric indications (Bridge et al., 2007). RCTs are considered the 'gold standard' for establishing efficacy and safety of new drugs.

However, participants in RCTs may not be representative of the general patient population, and individual trials may be unable to detect rare or delayed adverse or protective medication effects because of the relatively small sample sizes and short follow-up periods required to test efficacy outcomes (Vitiello et al., 2003). Dose titration may also be an issue, as study investigators may increase the dose faster than might be done in clinical practice. Given these limitations, a growing number of pharmacoepidemiological studies have examined suicide related risks associated with antidepressant exposure since the FDA and British Medicines and Healthcare Products Regulatory Agency (MHRA) advisories initially appeared in June 2003. Pharmacoepidemiology applies the methods of epidemiology to the study of effects and uses of drugs in large populations (Strom, 2006), thus providing a 'real-world' perspective on potential beneficial and adverse effects of medication treatment. This article will review recent pharmacoepidemiological studies (ecological, case-control, and cohort designs) that contribute to the antidepressant-suicidality debate in children and adolescents. The impact of regulatory warnings on changes in treatment and diagnosing patterns will also be considered, along with possible effects of these warnings on changes in rates of youth suicide.

## Method

A PubMed literature search of relevant English language articles was conducted (from June 2003 through August 2007) using various combinations of the MeSH keywords *antidepressants*, *child*, *adolescent*, *suicide*, *suicide attempt*, *case-control*, and *cohort*.

## Secular trends

If antidepressants pose an increased risk of suicide, then one would predict an increase in suicide rates to correlate with escalating pediatric antidepressant use during the past decade (Vitiello, Zuvekas, & Norquist, 2006; Zito et al., 2002). In fact, the majority of pharmacoepidemiological studies from several developed countries, including the USA, Sweden, Norway, and Denmark, have found inverse relationships between antidepressant prescription rates and youth suicide, suggesting that antidepressants have a protective effect on suicide risk (Isacsson & Rich, 2005).

Two USA studies focusing exclusively on pediatric populations found reduced suicide rates with increased antidepressant use. These studies differed in age range (10 to 19 vs. 5 to 14 years), statistical approaches (fixed-effects linear regression vs. case-mix adjusted random-effects Poisson regression), and exposure variables (antidepressants in general vs. SSRIs in particular), strengthening the validity of the findings. Olfson, Shaffer, Marcus and Greenberg (2003) examined suicide rates among youths aged 10 to 19 years and changes in antidepressant prescriptions in 588 regions of the USA between 1990 and 2000. For each 1% increase in antidepressant prescriptions, there was a decrease in the suicide rate of 0.23 per 100,000 adolescents per year, controlling for regional racial composition, median income, and physicians per capita. Gibbons, Hur, Bhaumik and Mann (2006) used national county-level suicide data in the USA and found that suicide rates among children ages 5 to 14 during the period 1996-1998 were lower in counties with higher numbers of SSRI prescriptions, controlling for sex, race, income, and access to mental healthcare.

## Population registry studies

Two studies using population-based Scandinavian registries do not support the hypothesis that SSRIs increase the risk of suicide in young people. Isacsson and Rich (2005), in a nationwide Swedish register study using all the forensic toxicological investigations of suicide from 1992-2000, reported that SSRIs had not been detected among any of 52 suicide completers younger than 15 years,

although 7 children were exposed to other antidepressants. Among adolescents aged 15 to 19 years, treatment with SSRIs was associated with a lower relative risk (RR) of suicide when compared with non-SSRIs (RR = 0.14, 95% CI = 0.05-0.43). Sondergard, Kvist, Anderson and Kessing (2006), in a nationwide Danish register-linkage study including all youths aged 10 to 17 years treated with antidepressants from 1995-1999, found that among 42 suicides, none was treated with SSRIs within 2 weeks prior to suicide. While an increased risk of suicide in youths treated with SSRIs compared with those not treated with SSRIs was reported in a crude analysis (RR = 19.21, 95% CI = 6.77-54.52), an analysis that adjusted for psychiatric hospital contact (a marker of illness severity) was no longer significant (RR = 4.47, 95% CI = 0.95-20.96), although the trend was in the direction of increased risk. Findings from these two reports support other toxicological investigations of suicide in adolescents that show very few suicide completers test positive for antidepressants at autopsy (Leon et al., 2006).

## Case-control studies

In the only reported case-control study to compare whether suicide attempts and completed suicide were associated with antidepressant medication exposure vs. no exposure, Olfson, Marcus and Shaffer (2006) found that the rate of antidepressant use was significantly greater (45.6%) in 263 children and adolescents aged 6 to 18 years attempting suicide after hospital discharge than in 1241 youths not attempting suicide (36.1%; OR = 1.52, 95% CI = 1.12-2.07); no association was observed among adults aged 19 to 64 years. Venlafaxine conferred the highest risk of suicide attempt among any of the newer antidepressants, in accord with findings from recent meta-analyses (Bridge et al., 2007; Hammad et al., 2006). Youths treated with antidepressants were also significantly more likely to complete suicide (OR = 15.62, 95% CI = 1.65-infinity), although the finding was based on only 8 suicide deaths and should be regarded as preliminary. The authors took many steps to control for confounding by indication, including a focus on a relatively homogeneous sample of Medicaid patients who had been treated for depression in an inpatient setting, and by matching cases and controls for age, sex, race/ethnicity, state providing Medicaid services, substance use disorder, recent suicide attempt, and treatment with psychotropic medications other than antidepressants. However, the authors were not able to control for other specific clinical factors that might have impacted on the likelihood of antidepressant prescription, such as severity and

duration of depression, persistence of suicidal ideation and long-term history of suicide attempts.

Two nested case-control studies using the UK General Practice Research Database (GPRD) found that risk of suicide and suicidal behaviour for adults treated with SSRIs was no greater than the risk with TCAs, although the evidence was mixed for younger patients. Martinez et al. (2005) examined self-harm behaviour and suicide in 146 095 patients with a new diagnosis of depression and exposed to either SSRIs or tricyclic antidepressants (TCA). Overall, there was no difference in risk of suicide in SSRIs compared with TCAs, but there was an increased risk of self-harm behaviour in patients 18 years old and younger prescribed SSRIs (OR = 1.73, 95% CI = 1.10–2.72). This difference persisted even after adjusting for severity of depression and other potential clinical confounders (OR = 1.59, 95% CI = 1.01–2.50). Jick, Kaye, & Jick (2004) reported no significant association between the use of any particular antidepressant (fluoxetine, paroxetine, amitriptyline vs. dothiepin) and risk of suicidal behaviour. Moreover, there was no evidence of a moderating effect of age. In fact, of 17 patients who committed suicide, none occurred among patients aged 10 to 19 years. Although 15 adolescent suicides were reported in the GPRD during the study period, no patient received an antidepressant medication, raising the critical issue of risk of untreated depression on suicide potential (Brent, 2004).

### Cohort studies

Valuck et al. (2004) conducted a cohort study in the USA of more than 24 000 paid health insurance claims for adolescents aged 12 to 18 years who were either newly diagnosed with MDD, had a prescription for antidepressant medication, or both, between January 1997 and March 2003. Treatment with SSRIs was not significantly associated with risk of suicide attempt after adjusting for potential confounding by indication (hazard ratio (HR) = 1.59, 95% CI = 0.89–2.82) (Valuck et al., 2004). Adolescents treated for more than 180 days with antidepressants were also less likely to make suicide attempts than those treated for less than 55 days (HR = 0.34, 95% CI = 0.21–0.55). In a Finnish study, Tiihonen et al. (2006) used data on 15 390 patients (152 587 person-years) who had been hospitalized for any reason. Among the subgroup of patients aged 10 to 19 years who had ever used an antidepressant, current antidepressant use was associated with an increased risk of attempted suicide (adjusted RR = 1.84, 95% CI = 1.40–2.42; SSRIs, RR = 1.91, CI = 1.43–2.55), but not with an increased risk of completed suicide. With respect to all-cause mortality, paroxetine use among 10 to 19 year olds

was associated with a greater risk of death (RR = 5.44, 95% CI = 2.15–13.73). Coincident with this observation, an analysis of RCT data found paroxetine to have the least favourable benefit-to-risk profile for treating pediatric depression (Bridge et al., 2007).

### *Timing of suicidal behavior in relation to antidepressant exposure*

The question of whether or not antidepressants increase the risk of suicide or suicidal behaviours in children and adolescents shortly after starting treatment has been examined in two studies from Group Health Cooperative, a large prepaid health plan in the USA. Simon et al. (2006) examined the association between antidepressant use and suicide and suicide attempts in 82 285 episodes of depression involving 65 103 patients who were prescribed an antidepressant between January 1992 and June 2003. Adolescents had a four-fold higher risk of suicide attempt than adults (314/100 000 vs. 78/100 000). However, as with adults, the highest risk was in the month *before* starting treatment and actually decreased by 60% after patients started medication. Subsequently, Simon and Savarino (2007) compared the rate of suicide attempts in the 90 days before and the 180 days after beginning antidepressant or psychotherapy treatment and again found the incidence of suicide attempt in adults and patients younger than 25 years to be highest in the month before starting treatment. Moreover, the same pattern in the timing of suicide attempts was found among patients receiving antidepressants from a primary care doctor, from a psychiatrist, and those receiving psychotherapy.

### **Impact of regulatory warnings on antidepressant prescribing**

Six studies find significant reductions in antidepressant prescribing to pediatric patients following UK and US regulatory warnings reporting risks of suicidality associated with use of antidepressants (Table I). There is also some emerging evidence that FDA advisories intended for pediatric patients taking SSRIs may have had spillover effects on community treatments for adults with depression (Valuck et al., 2007).

### **Impact of regulatory warnings on youth suicide rates**

In the USA, suicide rates among children and adolescents 19 years and younger rose 18.2% between 2003 and 2004, the first significant increase in youth suicide in more than a decade and the largest one-year change in the suicide rate in a

Table I. Published studies examining effects of regulatory warnings on prescribing and diagnosing patterns in children and adolescents.

Study	Country	Age range	Setting	Regulatory action	Results/comments
Murray et al. (2005)	UK	≤18 years	Primary care, January 2000 to December 2004	2003 UK regulatory advice contraindicating use of antidepressants (other than fluoxetine) in children and adolescents <18 years	35% decrease in contraindicated antidepressant prescription prevalence between 2002 and 2004, but only a 10% increase (NS) in fluoxetine use.
Kurdyak et al. (2007)	Canada	<20, 20–65, >65 years	Ontario Drug Benefit Program, April 1998 to March 2005	Five warnings in the UK, US, and Canada about risk of suicidal behavior during antidepressant treatment	UK warning about use of paroxetine resulted in an immediate 54% reduction in new paroxetine prescriptions for patients <20 years. No warning had an effect on new prescriptions for SSRIs as a group in any age category.
Nemeroff et al. (2007)	US	<18, 18–25, ≥26 years	Retail pharmacy prescription and physician audit databases, June 2000 to March 2005	October 2003 and March 2004 FDA advisories cautioning about use of antidepressants in pediatric patients	Antidepressant prescribing to patients <18 years decreased an average of 4% per month after the advisories. Psychiatrists were more likely than generalists to provide care for patients <18 years after the FDA warnings, a significant shift of care from pre-advisory levels. A slight increase in prescribing non-SSRIs was observed.
Libby et al. (2007)	US	5–18 years	National integrated claims database of managed care plans, October 1998 to September 2005	October 2003 FDA advisory (see above)	Proportion of patients receiving no antidepressant after initial depression diagnosis increased to 3-fold the rate predicted by data preceding the FDA advisory. SSRI prescription fills were 58% lower than predicted by the preadvisory trend. National rates of diagnosing depression significantly decreased among non-pediatrician primary care physicians, were unchanged for pediatricians, and increased significantly among psychiatrists (but not enough to offset the decline in primary care physicians).
Kurian et al. (2007)	US	2–17 years	Tennessee Medicaid, January 2002–September 2005	December 2003 UK warning and October 2004 FDA “black box” warning	33% decrease in new prescriptions of antidepressants in the 21 months after versus the 24 months before the UK warning, limited to non-tricyclic antidepressants. In contrast, new users of fluoxetine increased 60%. No increase in discontinuation of antidepressants or substitution with other psychotropic medications was observed.
Gibbons et al. (2007)	US & Netherlands	≤19 years	IMS Health retail pharmacy prescription database (US); PHARMO retail pharmacy prescription database (Netherlands)	October 2003 FDA advisory and December 2003 UK warning	From 2003 to 2005, 30% decrease in new SSRI prescriptions and 20% decrease in overall SSRI prescriptions in US and 22% decline in SSRI prescription rate in the Netherlands.

quarter century (the second largest change being an 11.1% decrease in suicide between 1998 and 1999) (Centers for Disease Control and Prevention, 2007; Hamilton et al., 2007). When the data in 10 to 24 year olds were examined by gender and age group, females aged 10 to 14 years had the largest increase in suicide rate (75.9%), followed by females aged 15 to 19 years (32.3%) and males aged 15 to 19 years (9.0%) (Lubell, Kegler, Crosby, & Karch, 2007). The increase in suicide rate after the regulatory warnings was also pronounced in The Netherlands, where a 49% increase in youth suicide rate from 2003 to 2005 coincided with a 22% decrease in SSRI prescription rate during the same time period (Gibbons et al., 2007). Some experts contend that the sharp rise in youth suicide is the direct result of boxed warning labels placed on antidepressants and the subsequent decline in antidepressant prescriptions (Couzin, 2007). However, it is premature to draw causal conclusions about a one-year 'spike' in the youth suicide rate until data from several consecutive years are available for comparison.

### Conclusions and recommendations for the future

Ecological studies suggest that increases in antidepressant prescriptions are associated with declines in youth suicide, but naturalistic epidemiological data cannot establish causal links. Scandinavian registry studies also show no consistent association between antidepressant use and suicide. On the other hand, one case-control study indicates that antidepressants increase the risk of suicide attempts and suicide in children and adolescents but not adults, while two cohort studies provide mixed evidence. The period of greatest risk for suicide and suicide attempt appears to be in the month before starting antidepressant treatment and is rare following the initiation of antidepressants. The seemingly contradictory findings of the observational studies reviewed here can probably best be explained by limitations to adequately control for confounding by indication (i.e. the decision to prescribe an antidepressant may be associated with factors that are also associated with an increased risk of suicidality), which would lead to erroneous conclusions about causal links between drug exposure and outcomes.

Future pharmacoepidemiological studies should therefore aim to prospectively assess the safety of antidepressants for pediatric indications. Registries of patients beginning antidepressant treatment could be used to collect extensive baseline data on demographic and clinical characteristics of patients (e.g. illness severity, diagnostic comorbidity) and systematically track actual use of medication and

outcomes over time. A longitudinal database of well-characterized patients would permit judicious use of propensity-score approaches and other more traditional statistical and epidemiological (restriction, matching, stratification) techniques to control for confounding, thus reducing the likelihood of obscure results due to incomplete clinical information from administrative databases (Hunter, 2006). However, until these studies can be performed, the current generation of pharmacoepidemiological studies provides some valuable information to inform clinicians, patients and families about the antidepressant/suicidality issue.

Finally, the proportion of pediatric patients receiving pharmacological treatment for depression dropped sharply after the FDA advisory with no concomitant increase in alternative treatments. Empirical work is needed to evaluate the impact of regulatory warnings on youth suicide.

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