THINKING OUTSIDE THE BLACK BOX: THE RELATIVE RISK OF SUICIDALITY IN ANTIDEPRESSANT USE

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The Food and Drug Administration issued a black box warning in response to concerns that antidepressants may increase the risk of suicidality in children and young adults. In the effort to weigh the benefits and risks of antidepressants, numerous methodological challenges preclude the determination of a definitive answer. The available empirical findings are mixed, with some studies displaying an association between antidepressant use and reduced suicidality, and other studies uncovering a significant risk of suicidality for patients treated with antidepressants compared to placebo. In the absence of more conclusive information regarding the relative safety and efficacy of antidepressant medication, frequent monitoring, especially during the first weeks of treatment, should be a component of all treatment plans. Further research is needed to determine which patients might benefit most from antidepressant treatment, as well as whether the black box warning has prevented suicide, or merely hindered the prescription of potentially helpful medication.

Keywords: Black box warning, antidepressants, suicide, depression

In 2003, 32,488 people committed suicide in the United States (Hoyert, Heron, Murphy, & Kung, 2006). Though suicide is a problem for individuals across the lifespan, suicide rates among youth and young adults are especially disturbing. Suicide was the second leading cause of death among 25-34-year-olds in 2005 (behind only unintentional injury), and the third leading cause for 10-14-year-olds (behind unintentional injury and malignant neoplasms) and 15-24-year-olds (behind unintentional injury and homicide; Centers for Disease Control and Prevention, 2003). With such a substantial number of deaths attributed to suicide, it is no surprise that considerable research has been dedicated to determining the most common and potentially preventable causes of suicidal behavior.

Major mood disorders that are untreated or unresponsive to treatment are associated with suicide and self-harm (Angst, Angst, & Stassen, 1999). In a study examining suicidal ideation and behaviors across 17 countries, Nock et al. (2008) found that the strongest diagnostic risk factor for suicidal ideation, plans, or attempt in high-income countries was the presence of a mood disorder. Major Depressive Disorder (MDD), specifically, affects a significant proportion of the population, with the lifetime prevalence of the condition estimated to be 16.6% (Kessler et al., 2005). With depression being identified as such a salient risk factor in suicidal ideation and behavior, treatment for depression constitutes an important suicide prevention strategy.

Antidepressant medications are frequently prescribed for the treatment of depression. As the prescription and use of antidepressants has increased (Stagnitti, 2008), so has attention to possible negative effects from these medications. Over the last decade, significant media coverage of suicide has brought increased scrutiny to this problem, particularly a potential relationship between suicide and antidepressant medications. Sharp and Chapman (2004) conducted a Lexis-Nexis search for "antidepressants" and "suicide" in major newspapers from 2000 through part of 2004, uncovering a substantial increase in the number of articles containing these keywords over the specified years. Although some media reporting of the risk of suicide when taking antidepressants has been responsible and reflected research findings in an accurate way (e.g., Berenson & Casey, 2007; Vedantam, 2006), other in-

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stances of coverage have either distorted results or focused on emotional case reports rather than scientific findings. For example, an article in the *New York Times Magazine* detailed the emotional pains experienced by a teen's parents after his suicide (Mahler, 2004). In this emotive portrayal, the parents insisted that a recent prescription of sertraline was to blame. Though the article examines various viewpoints, including emphatic praise by youth who feel they have been "saved" by antidepressants (which does not appear until the end of the lengthy commentary), there is still an apparent slant toward the emotional struggle of the surviving family rather than empirical research bearing on the issue. This is not meant to discount the pain the suicide has caused the family, but rather to draw attention to the paucity of balanced reporting in the media. There is an inherent asymmetry to media coverage: There are reports of suicides potentially caused by antidepressants, but it is practically impossible to identify suicides prevented by antidepressants. Furthermore, Sharp and Chapman (2004) noted that only half of the randomly selected major newspaper articles with headlines containing "antidepressant" and "suicide" in early 2004 provided a balanced description of the antidepressant and suicide controversy. Also, just half of the randomly selected articles discussed the risks of untreated depression and other psychological disorders. Given the much wider audience of common media outlets than scientific journals, the media's influence on popular beliefs can be vast and powerful.

The Food and Drug Administration (FDA) has both reacted to the media's reports and fueled them by initiating efforts to investigate the role of antidepressant use in suicidality. The FDA Modernization Act of 1997 resulted in pharmaceutical companies receiving an incentive (extended patent life) in exchange for conducting clinical trials of certain medications in children, some of which were antidepressants. This resulted in an increase in randomized clinical trials (Vasa, Carlino, & Pine, 2006). In 1998, the FDA further required manufacturers to evaluate the safety and efficacy of new medications if doctors were expected to prescribe these medications to minors. In response to increased media attention about antidepressants and youth suicide, as well as newer research suggesting a potential increase in risk of suicide, the FDA issued a black box warning in 2004, exhorting caution when prescribing antidepressants to youth. The black box warning is the strongest labeling warning the FDA issues for approved medications; it places information about the potential risks of using the medication on the product labeling. According to the FDA (2007), the initial text of the package insert reads, in part, as follows:

> Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [insert established name] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. (p. 1)

Does this warning achieve more harm than good? Essentially, there are two kinds of error that may be associated with the prescription of antidepressants. First, there is the danger of underprescribing the medication, prescribing an insufficiently low dose (or none at all) relative to what would be an optimal dosage. Conversely, it is possible to overprescribe the medication when a lower dose (or none at all) would be optimal. Presumably, the FDA's goal in mandating the black box warning was to protect consumers from an increased risk of suicidal behaviors. However, efforts to increase protection can cut both ways. It is not necessarily the case that warnings yield a net benefit. A warning could shift the balance of errors toward underprescribing, and the costs of such a shift might outweigh the benefits. For example, if antidepressants do in fact increase the risk of suicide, preventing a small number of suicides through lower doses or fewer prescriptions could be outweighed by a larger number of suicides resulting from insufficient treatment of depression for many patients.

Regarding the research findings, studies have found mixed results in terms of whether antidepressants precipitate or prevent suicidal behavior in adults and children. Gaudiano and Epstein-Lubow (2007) briefly review some research on this topic, but we hope to present a more detailed account of the literature including methodological concerns. Generally, physicians prescribe antidepressant medications with the intention of lessening the duration and intensity of a depressive episode. Because the treatments for which antidepres-

sants are indicated often carry an increased risk of suicide, it can be difficult to determine whether the prescription or actual usage of antidepressants affects this risk, and if so, whether it raises or lowers the risk. The fundamental controversy over the black box warnings relates to whether the benefits of prescribing antidepressants outweigh the risks, as well as what steps, if any, the FDA should take in making recommendations for or against the prescription of these medications for some or all populations of patients.

RESEARCH CHALLENGES

Though research on the potential role of antidepressants in suicide is imperative, a multitude of methodological challenges complicate the interpretation of existing studies and the design of new ones. One significant challenge is the lack of consistent or relevant outcome measures. Though suicidal ideation is troubling to both the ideator and those who care about him or her, thinking about suicide is not quite as problematic as attempting it, let alone successfully completing it. Indeed, Nock et al. (2008) found a cross-national ideation rate of 9.2%, but an attempt-planning rate of only 3.1% and an even lower actual attempt rate of 2.7%.

On a related note, the operational definition of "suicidality" is critical. This varies widely from study to study, and usually this is not restricted to actual completed suicides. In fact, as will be documented in greater detail below, some studies—even large ones—do not involve cases of actual suicides. This crucial point often is overlooked by nonspecialists who report or comment on the potential link between antidepressants and suicide (Bostwick, 2006; Klein, 2006; Nishawala, Boorady, & Koplewicz, 2006; Posner, Oquendo, Stanley, & Gould, 2004). Other problems with operational definitions include the delineation of children and adults in pediatric trials (Bostwick, 2006); age boundaries are often ill-defined and inconsistent across studies.

Another difficulty in performing the most informative randomized trials is ethical in nature: It may be irresponsible to prescribe placebos to deeply depressed and suicidal patients (Goldney, 2006; Rihmer & Akiskal, 2006). Ethics aside, there are pervasive problems evident even in studies that do not include placebo controls for severely depressed individuals. The low base rates of completed suicide pose a particularly notable challenge. Gunnell, Saperia, and Ashby (2005) calculated several estimates regarding sample sizes necessary to identify the effect of selective serotonin reuptake inhibitors (SSRIs) on the risk of suicide. Setting 20% risk reduction as the threshold for clinical significance, Gunnell et al. calculated that 1.9 million participants would be needed to achieve 80% statistical power to detect a clinically significant decrease in suicide risk at the usual .05 significance level. A comparably massive sample would be required to detect a clinically significant increase in suicide risk, and it is unlikely that investigators will be able to collect good data on such a large sample. Meta-analyses have greater potential to accumulate such a sample size, but definitional and measurement discrepancies across studies would contribute to the heterogeneity of effects, and therefore an even larger total *N* would be required to detect effects.

Furthermore, though randomized clinical trials are considered the "gold standard" for treatment assessment, recruitment procedures often preclude generalizable findings due to sampling methods. Exclusion criteria customarily prevent patients with the full range of depressive severity and suicidality from being recruited, which limits generalizability of findings. Patients in clinical trials may not represent the overall population of patients who are prescribed antidepressants, as high-risk participants may be excluded or defined differently from trial to trial (Bostwick, 2006; Vasa, Carlino, & Pine, 2006). Even within clinical trials, patient compliance with medication and variance in dosage would make translation from controlled studies to antidepressant use in the "real world" a challenge. There is also the problem of failure to follow the doctor's prescription, including the possibility of premature termination of the medication. Because one cannot safely assume that prescribed medicines are taken as instructed, the external validity of research relying on prescription data is limited.

Naturalistic, observational studies avoid some of the problems with controlled experiments, but they introduce some of their own pitfalls. Naturalistic studies suffer from the problem that the severity or nature of depression and suicidality tend to be confounded with type or amount of treatment. It is practically impossible to separate these factors in observational research. Nonetheless, naturalistic studies are common in the research literature, making it important to determine what sort of conclusions can be reasonably drawn from this type of investigation, and prompting the design of more controlled research studies based on hypotheses deigned from naturalistic findings. One noteworthy strength of this type of study, however, is that it does not exclude participants with previous suicidal behavior, which is something that occurs in many clinical trials.

Yet another research challenge is the need to control for prior risk of suicide. Patients seeking antidepressant medication may already be on a "downward trajectory" and could already be at a higher risk for suicidality before taking the medication. Many studies have not taken previous ideation into account (Nishawala et al., 2006). Even when it is assessed, it is difficult to determine how this translates into suicide risk.

Failure to accurately disclose funding amounts and sources has become a phenomenon of recent interest, as multiple prominent researchers in psychiatry departments across the United States have faced investigation over a lack of disclosure. This is particularly concerning, as conflicts of interest have the potential to create bias in the design of research trials, as well as reporting of results. Kjaergard and Als-Nielsen (2002) examined all randomized clinical trials published in the *British Medical Journal* (which requires authors to report funding sources and competing interests) from 1997 to June 2001, finding a relationship between trials funded by for-profit organizations and positive author conclusions in favor of the experimental intervention. A relationship between study sponsorship and reported results has also been identified more specifically for SSRI trials, though more research is needed for a more comprehensive group of antidepressant medications (Baker, Johnsrud, Crimson, Rosenheck, & Woods, 2003). Additionally, coverage of pharmacological research in the general news media frequently fails to identify industry sponsorship of the trials being reported (M. Hochman, S. Hochman, Bor, & McCormick, 2008), further complicating the results presented to the consumers seeking and receiving treatment.

Finally, it is unclear how well the findings from research with adult participants generalize to child and adolescent populations. The data on efficacy and side effects of antidepressants in children is even more limited than what is available for adults. Although there are some discrepancies in findings for adults, the literature for children is more mixed, difficult to interpret, and controversial. It may not be safe to generalize the findings of adult antidepressant studies to children unless the physiological and psychological processes affected by antidepressants, the alleviation of MDD, and suicidality are common between adults and children (Vasa et al., 2006). The similarity of these relationships across children and adults has not been demonstrated convincingly. For example, Nishawala, et al. (2006) suggested that children may be especially susceptible to a quick withdrawal reaction if a dose is missed, even by a few hours. In addition, serotonergic functioning may differ from adults to children, and metabolism rates may cause differences in the actual half-life of the medications. Nishawala et al. suggested that adolescents should be studied separately from children to gain more insight into these variations.

EVALUATION OF THE RESEARCH LITERATURE

Bearing in mind each of the methodological caveats described above, we turn now to an overview of the pertinent empirical research. Table 1 summarizes the studies cited and discussed in this section.

Are Antidepressants Efficacious?

There has been some controversy over whether antidepressant medications truly outperform placebo, which has been highlighted in the media as well as in the empirical literature and requires further research attention (Gaudiano & Herbert, 2003). Nonetheless, several randomized controlled trials have established the efficacy of antidepressants for the treatment of major depression in adults (Williams et al., 2008). In spite of the possible differences between adults and children, some studies have found data supporting the efficacy of SSRIs on youth, as well (Cheung, Emslie, & Mayes, 2006; Emslie et al., 2002; Keller et al., 2001; Wolraich, 2003). For children, however, fluoxetine is the antidepressant with the strongest empirical support for treatment of depression (Hegerl, 2006; Usala, Clavenna, Zuddas, & Bonati, 2008). As a result, it is often considered the medicinal treatment of choice (Kratochivil, Vittiello, Brent, Bostic, & Naylor, 2006) and, at present, fluoxetine is the only antidepressant approved by the FDA for use with pediatric depression (Nishawala, et al., 2006).

Do Antidepressants Cause Suicide/Suicidality?

Yes. Meta-analyses of randomized controlled trials (RCTs) comprise the strongest argument for the idea that antidepressants cause suicide in pediatric patients. Hammad, Laughren, and Racoosin (2006) as well as Goodman, Murphy, and Lazoritz (2006) conducted meta-analyses of the data used by the FDA in determining the need for a black box warning. The meta-analyses consisted of data from 24 child and adolescent studies (23 placebo-controlled trials plus the Treatments for Adolescents with Depression Study [TADS]), totaling over 4000 subjects.

Table 1

Summary of Studies Investigating Links between Antidepressants and Suicidality

Authors	Methodology	Number of subjects	Age of subjects	Definition of suicidality	Definition of antidepressant use	Classes of antidepressants	Results
Bridge et al. 2007	Meta-analysis of RCT data	5,310	5-18	Suicide attempt, suicidal ideation, preparatory actions toward imminent suicidal behavior	Randomization to antidepressant condition	SSRI, nefazodone, venlafaxine, mirtazapine	No completed suicides; increased risk of suicidal ideation/attempt for antidepressant vs. placebo
Fergusson et al. 2005	Meta-analysis of RCT data	87,650	Unspecified (presumed all ages)	Suicide attempts (fatal and non-fatal)	Randomization to antidepressant condition	SSRI (some with non-SSRI as controls)	SSRI use related to increased suicide attempts; SSRI use not related to completed suicides
Goodman et al. 2006	Meta-analysis of RCT data	4,400	Child and adolescent	suicide attempts, actions made in preparation for immediate suicide attempt, and suicidal ideation	Randomization to antidepressant condition	SSRI, SNRI, atypical*	Stronger relationship between antidepressant use and suicidal ideation to placebo groups.
Gunnell et al. 2005	Meta-analysis of RCT data	40,826	Adults	Suicidal thoughts, non-fatal self-harm, suicide	Randomization to antidepressant condition	SSRI	No relationship between antidepressants and suicide or suicidal thoughts; "weak" evidence of relationship between antidepressants and self-harm
Hammad et al. 2006	Meta-analysis of RCT data	4,582	Pediatric	primary: attempt, preparatory actions, ideation; secondary: the previous 3 + self-injury with intent unknown and injury events cause unknown; suicide items on depression scales	Randomization to condition	Multiple (9)	No completed suicides; increased pooled risk differ for all indications of drugs vs. placebo but not statistically significant; no increased suicidality as shown by depression
Wohlfarth et al. 2006	Meta-analysis of RCT data	4,000+	Unspecified (pediatric)	Completed suicides, suicide-related events (terms with "suic-" prefix), self-harm/hostility/emotional ability	Randomization to antidepressant condition,	SSRI, SNRI	no completed suicides more "suic-" events and more "other" events in treatment group as compared to placebo; significant risk difference for MDD but not anxiety disorders
Bauer et al. 2006	Non-randomized treatment study	425	15+	Combination of suicidal ideation on monitoring form, documented adverse events including completed suicide hospitalization for suicide attempt, or suicidal ideation requiring clinician intervention	"clinically significant increase" in antidepressant dosages between assessments	All	increased antidepressant exposure not related new-onset suicidality in to patients with bipolar disorder
Gibbons et al. 2007	Ecological (linked)	226,866	18+	Suicide attempts	Prescriptions dispensed within VA system	SSRI, "new-generation non-serotonergic-specific," TCA rate	Lower suicide attempt related to antidepressant use
Søndergård et al. 2006a	Ecological (linked)	1,512,487	18+	Completed suicides	# of antidepressant prescription purchases	SSRI, other "new-generation," and older antidepressant	Patients who purchased SSRIs or newer antidepressant twice or more had lower suicide risk than those who purchased once
Søndergård et al. 2006b	Ecological (linked)	51,731	10-22	Completed suicides	Antidepressant purchase (DDD)	SSRI, other "new-generation," and older	No statistically significant relationship between SSRI use and completed suicide

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Authors	Methodology	Number of subjects	Age of subjects	Definition of suicidality	Definition of antidepressant use	Classes of antidepressants	Results
Bramness et al. 2007	Ecological	Entire country (Norway)	All	Completed suicides	Antidepressant sales (DDD)	SSRI, TCA, "other"	Relationship between increase in sales of non-TCAs and decrease of suicide rates
Gibbons et al. 2005	Ecological	Entire country (US)	5+	Completed suicides	Number of pills prescribed at sample of retail pharmacies	SSRI, TCA, "other" (nefazodone, mirtazapine, bupropion, and and venlafaxine	No relationship between antidepressant and suicide, but inverse relationship between non-TCAs and suicide and positive relationship between TCAs and suicide
Gibbons et al. 2006	Ecological	Entire country (US)	5-14	Completed suicides	Number of pills prescribed per person	SSRI	Increased SSRI prescriptions related to lower suicide rates
Hall et al. 2003	Ecological	Entire country (Australia)	15+	Completed suicides	Antidepressant sales (DDD); estimated sales by age and gender by results of prescriber survey	All	Groups with highest increase in antidepressant use showed highest decrease in suicide rate
Kalmar et al. 2008	Ecological (Hungary)	Entire country (youngest group >20)	Unspecified	Completed suicides	Filled prescriptions (DDD)	All	Increased antidepressant use related to decrease in suicide rate
Korkeila et al. 2007	Ecological (Finland)	Entire country	All	Completed suicides	Reimbursed prescriptions (DDD)	All	Increased antidepressant use related to decrease in suicide rate
Nakagawa et al. 2007	Ecological	Entire country (Japan)	Unspecified (includes under 19)	Completed suicides	Antidepressant sales from 99% of retail pharmacies in Japan converted to defined daily dose	"Newer" (SSRI, SNRI), TCA and "other"	For newer and SSRI, as presumed antidepressant use increased, suicide rate decreased
Olfson et al. 2003	Ecological	Unspecified	10-19	Completed suicides	Antidepressant Prescription filled	All	Increase in antidepressant prescription related to decrease in suicide rate
Simon et al. 2006	Ecological	65,103 (presume all)	Unspecified	Completed suicides and attempts resulting in hospitalization	Prescriptions filled	"Newer," "Older"	Risk of suicide attempt highest before treatment and declined after taking antidepressants; increase in risk of suicide attempt only for older antidepressants

Note. DDD = defined daily dose; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

Antidepressant drug manufacturers were provided with search strings to identify "suicide related events", which were then grouped into categories by suicidology experts at Columbia University. The primary suicidality definition for these meta-analyses consisted of suicide attempts, actions made in preparation for immediate suicide attempt, and suicidal ideation, though Hammad et al. also included a secondary definition, used in follow-up analyses, including self-injury or ambiguous injury in addition to the items included in the primary definition. (There was no difference in the risk estimates between the primary and secondary suicidality outcomes.) No completed suicides occurred in any of the trials included in the meta-analyses. However, after setting aside trials in which no suicide-related events occurred, both meta-analyses found that antidepressant use in a pediatric sample was associated with a slightly increased risk of suicidality compared to patients in a placebo condition.

Based on the results of a meta-analysis of 22 studies (N>4,000), Wohlfarth et al. (2006) argued that doctors should be watchful when prescribing SSRIs, SNRIs, and other antidepressants to younger patients. In this study,

suicide-related events were defined as terms with a "suic-" prefix. For youth with MDD, a significant risk difference for suicide-related events (though not actual completed suicides) was found. The authors posited that antidepressants might be more effective for children with severe and prolonged depression. Furthermore, the authors concluded that antidepressants appeared to be efficacious for child anxiety, but the results for depression were not quite as conclusive. Therefore, the benefits of antidepressants in pediatric populations may outweigh the risks, but only in the case of anxiety disorders and not depressive disorders. Presuming that the risk of harm from overprescribing outweighs the risk of harm from underprescribing, Wohlfarth et al. recommended that warnings be issued because of an increased risk of suicidality with the use of antidepressants in children, and that these warnings be issued for all antidepressants until contradictory facts are found.

In another pediatric meta-analysis of RCT data, Bridge et al. (2007), evaluated 27 trials (N=5,310) of antidepressants for youth with MDD, obsessive-compulsive disorder (OCD), and non-OCD anxiety disorders. Bridge et al. defined suicidality as suicide attempt, suicidal ideation, or preparatory actions toward imminent suicidal behavior. When combining all trials, there was an increased risk of suicidal ideation/attempt, albeit small, associated with antidepressant use.

Fergusson et al. (2005) conducted a meta-analysis of 702 trials (N=87,650), of SSRIs vs. placebo or active control, looking at subjects of all ages. The primary outcome measure in this analysis was fatal and non-fatal suicide attempts, with the use of "suicide" in describing a non-fatal attempt required for inclusion, with the exception of the term, "overdose." SSRI use was associated with a statistically significant increase in the odds of a suicide attempt when compared to placebo or other non-tricyclic therapeutic interventions. Their analyses indicated an absolute risk difference of 5.6 suicide attempts between every 1000 patient-years of SSRI use and placebo, which the authors note may be clinically significant when considering the number of antidepressants prescribed.

Focusing on adult patients, Gunnell, Saperia, and Ashby (2005), detected a small increased risk of self harm in a meta-analysis of RCT data including over 450 trials (N=40,826) of SSRI vs. placebo in adults, but this difference was not statistically significant. The process for defining self harm was not clear, and approximations were made in some cases. The authors called for larger trials with longer follow-up to enable more definitive findings.

In an ecological, non-RCT study, Gibbons, Hur, Bhaumik, and Mann (2005) found that tricyclic antidepressants (TCAs; defined as number of pills prescribed) were related to an increased suicide rate in the United States between 1996 and 1998, when examining data by county. The authors offer possible explanations for this finding, among them poorer overall mental health care in areas where TCAs were more frequently prescribed. In addition, TCAs are believed to be more toxic than SSRIs upon overdose.

In sum, the bulk of the argument that antidepressants cause suicide/suicidality rests in results from experimental studies. Experimental research provides researchers with the opportunity to establish causality under well-controlled conditions. However, it is important to recognize that the risk of suicidality in these studies was found to be greater than the risk of suicidality resulting from placebo, as opposed to being compared to the risk of receiving no treatment at all.

No. Naturalistic data comprises a strong portion of the argument for a lack of relationship, or even an inverse relationship, of suicide and antidepressant use. These ecological, non-controlled studies cannot establish causality between antidepressant prescription and suicide, but examining large-scale societal trends can be a practical research method yielding suggestive results and prompting further research. To test whether antidepressant medication prevents suicide, Søndergård, Kvist, Anderson, and Kessing (2006a) examined naturalistic, linked data comparing patients in Denmark who redeemed an antidepressant prescription once with those who redeemed prescriptions twice or more. Patients who redeemed prescriptions for SSRIs twice had a lower suicide rate than patients who redeemed prescriptions only once, suggesting that antidepressants may be useful in preventing suicide. However, this finding may more strongly indicate that the initial risk period for suicide when on antidepressants is in the first weeks, rather than supporting a general protective effect. It is also worth noting that people who sought out and were prescribed antidepressants were more likely to be depressed in the first place.

Nakagawa et al. (2007) conducted an ecological analysis of the relation between antidepressant prescription and suicide rates in Japan from 1999 to 2003. Results revealed annual decreases in the suicide rate when there were annual increases in the rate of antidepressant prescriptions, especially among males. Newer antidepressants, including SSRIs, were only first introduced in Japan in 1999, and with this introduction came a strong increase in the prescription of antidepressant medications there. In a similar observational study, Korkeila, Salminen, Hiekkanen, and Salokangas (2007) analyzed the relationship between trends in antidepressant prescription

and suicide rates in Finland between 1994 and 2001. The inverse relationship between prescription and suicide rate was also observed in this sample.

Kalmar et al. (2008) examined the relationship between prescription and suicide rates in Hungary, with additional examinations of age and gender differences. The authors found an inverse relationship between prescription and suicide rates for both genders, but no relationship for those less than 20 years of age and those 50-69 years of age or for women aged 30-49. The authors posited a protective effect of antidepressants on suicide in elder adults and acknowledged the limitations of the study design. They used the defined daily dose of medication to calculate the level of treatment, and though this is a more sophisticated calculation than some ecological samples, it does not necessarily provide an accurate assessment of the medication actually taken by patients because it assumes strict adherence to prescriptions. Bramness, Walby, and Tverdal (2007) found similar results in Norway: There was an inverse relationship between sales of non-tricyclics and suicide rates, though it was only statistically significant for low sales rates.

Looking at U.S. data by county, Gibbons, Hur, Bhaumik, and Mann (2005) found no overall association between the prescription of antidepressants and suicide after adjusting for age, sex, race, and county. Gibbons et al. also examined different classes of antidepressants.

SSRIs, non-SSRIs, and non-tricyclics had an inverse relation with suicide rate. In examining Veterans Health Administration data, Gibbons et al. (2007) found that the suicide attempt rate after initial treatment with an SSRI was lower than the rate for all other depressed patients. Analyzing data from 1992-2003, Simon, Savarino, Operskalski, and Wang (2006) found no significant increase in suicide or serious suicide attempts following the initiation of treatment with newer antidepressants. Rihmer and Akiskal (2006) observed a similar relationship in countries with traditionally high baseline rates of suicide, citing a decline in suicide rates upon the proliferation of antidepressant prescriptions, especially for women.

In a regional analysis of changes in antidepressant treatment and suicide rates, Olfson, Shaffer, Marcus, and Greenberg (2003) found that increased prescription of antidepressants was related to decreases in suicide rate, principally for males, older teens, and adolescents living in lower-income areas. Looking further at a pediatric population, Gibbons, Hur, Bhaumik, and Mann (2006) examined the relationship between antidepressant prescription and suicide rates in 5- to 14-year-olds from 1996 to 1998. There was an inverse relationship between SSRI prescription and suicide rates.

Søndergård, Kvist, Andersen, and Kessing (2006b) once again examined their Danish sample of naturalistic data. The prescription and use of SSRIs in children and adolescents increased over time, but the suicide rate stayed largely the same. Furthermore, none of the 42 completed suicides among 10- to 17-year-olds observed in Denmark during the time period covered by the study involved a child who had been treated with SSRIs within two weeks of the suicide.

Bauer et al. (2006) examined the risk of suicidality, defined as suicidal ideation, suicide attempt resulting in hospitalization, or completed suicide, in bipolar patients exposed to antidepressants and found no increased risk of suicidality as related to an increase in antidepressant dosage. This is an important finding because patients with bipolar depression are a population at high risk for suicidality (Rihmer & Pestality, 2002). Instead, new-onset suicidality was related to other factors, namely symptom ratings, neuroticism, and prior attempt (Bauer et al., 2006).

In addition to the body of naturalistic findings, some RCTs have shown that exposure to antidepressant medication does not increase suicide risk. In their meta-analysis of randomized controlled trials of SSRIs vs. placebo, Gunnell et al. (2005) found no increased threat of suicide in patients exposed to SSRIs. It was noted that some risks of suicide could have been present but may have been counterbalanced by protective effects of the medication. Furthermore, for youth with anxiety disorders, no significant risk between antidepressant use and placebo difference was found (Wohlfarth, 2006).

Though, as previously discussed, Fergusson et al. (2005) found an association between antidepressants and an increased rate of suicide attempts, it is important to note that suicide attempts, not completed suicides, were the focal point of this study. The authors reported that there was not a statistically significant increase in the number of completed suicides in these trials.

Overall, the bulk of the argument that antidepressant use is not related to suicidality is based in naturalistic findings, though some more controlled trials have also supported this argument. Naturalistic data compares antidepressant use to no treatment (or at least no psychopharmacological treatment). As noted earlier, the low base rate of completed suicide makes it difficult to study the outcome of greatest concern. Safer and Zito (2007) note that the substantial variation in reported suicide rates across countries, as well as over time and between demographic groups within countries, highlights the need for additional research. Despite the uncontrolled nature of naturalistic and epidemiological research, there does seem to be a trend such that when compared with

no treatment at all, antidepressants are related to a reduction in suicidality.

ALTERNATIVE EXPLANATIONS

Even when an increased risk of suicidality among individuals prescribed or taking antidepressant medication is found, alternative explanations must be considered. Patients may have unreasonable expectations for improvement, and when rapid improvement does not occur they may experience despondency or despair (Jick, Kaye, & Jick, 2004; Nishawala et al., 2006). A commonly cited phenomenon is that the risk of suicide rises as a depressed person first begins to feel better (Nishawala et al.). Treatment may increase physical drive and energy before a patient's cognitive symptoms of depression are alleviated. This increased drive may allow suicidal patients to enact plans they were previously unable to carry out. This can be a dangerous time for many people who recover from depression, regardless of the mechanism for improvement. Nishawala et al. noted that this risk is highest in the initial 10 days of treatment. However, the existence of this risk is not unequivocal. Joiner, Pettit, and Rudd (2004) did not find evidence of this particular phenomenon. Rather, they found that incomplete remissions were, on the whole, a risk factor for suicidality, and also an indicator of more severe depression in general. Thus, increased energy in the absence of other symptom improvement was not necessarily a key factor for increased suicidality, in and of itself. This idea requires further empirical inquiry.

Simon and Savarino (2007) examined the risk of suicide attempt in patients before and after treatment for depression, with the treatments including individual psychotherapy, antidepressant medication prescribed by a primary care physician, and antidepressant medication prescribed by a psychiatrist. The results revealed that the highest risk for suicide attempt occurred in the month before starting treatment, regardless of treatment type. The authors concluded that suicide risk is independent of prescribed medication or type of doctor doing the prescribing. Such findings are consistent with the possibility that medication itself is not causally relevant.

Despite the fact that there was a greater occurrence of suicidal thoughts and self-harm in youth treated with SSRIs when compared with placebo, none of the 4,400 patients in Gunnell and Ashby's (2004) study actually committed suicide. This fact is common to many studies: ideation occurs far more than attempt and completion. Other research has tested whether persons committing suicide had detectable levels of antidepressant medication in their bodies at the time of death. For the 49 suicides among 13- to 21-year-olds in Utah, no therapeutic or even sub-therapeutic level of an antidepressant was detected during autopsy (Moskos, Olson, Halbern, Keller, & Gray, 2005). This raises the possibility that noncompliance with prescriptions or subtherapeutic doses could be factors in suicidal behavior. Had these 49 youths been prescribed an appropriate dose of an antidepressant and taken the medication as instructed, this may have prevented some of their suicides. This is speculative, of course, yet the uniform absence of antidepressant medications during autopsy raises questions about the contribution of these medications in the instances of suicide among youth. As noted earlier, relying on prescription data can be problematic: Just because an antidepressant was prescribed does not mean that it was taken as instructed.

Another explanation for increased reports of suicidality in youth treated with antidepressants centers around anxiety. Hammad, Laughren, and Racoosin, (2006) posited that the rate of suicidal ideation for patients on antidepressants might actually be the same as those not being treated with antidepressants. The authors proposed that because antidepressants have shown some efficacy in treating child anxiety, children taking antidepressants may experience less social anxiety and thus would be more willing and able to verbalize their thoughts. The possibility that more frequent reports of suicidality among individuals taking antidepressants may stem from a propensity to disclose suicidal thoughts, rather than an increase in their actual frequency, requires empirical substantiation.

COST-BENEFIT ANALYSES

Weighing the costs and benefits of antidepressant treatment is no small feat, as the research literature is expanding rapidly and diversifying into new permutations of populations, medications, suicidality definitions, statistical analyses, and so on. Even in studies where antidepressants were related to an increase in suicidality risk, the authors sometimes conclude that the efficacy of medication and the resulting benefits outweigh the risks at least in some cases (e.g., Bridge, et al., 2007). Thus, it is difficult to render a definitive blanket recommendation regarding antidepressant prescriptions, and perhaps even more difficult for lay media coverage to describe the full picture in the typically short, perfunctory news reporting format.

RCT findings can be considered to be more internally valid than naturalistic findings, and it looks like many of the RCTs, especially in the case of younger patients, support the FDA's decision to express concern about antidepressants prescribed for youths. It is difficult to determine where to draw the line in terms of problematic side effects: Is an increase in suicidal ideation truly a problem if an increase in suicide attempts and completed suicides is not occurring? Findings in very large naturalistic studies generally do not show increases in completed suicides when antidepressants are prescribed.

For adults, the benefits of antidepressants have been shown to outweigh the risks for many patients. The research generally has found that antidepressants alleviate depressive symptoms and reduce the intensity and duration of depressive episodes. Nonetheless, all patients being treated for depression should be monitored for suicidality and agitation, especially within the first month of treatment. Because the risk of suicide is higher in the first weeks of antidepressant use than later in treatment, (though not before treatment), visits with the prescribing doctor in the beginning phase of treatment could attenuate despondency over delayed results as well as check for suicidal ideation and behavior. The increased influence of managed care may make it difficult to monitor patients more frequently, but it seems prudent to err on the side of caution until more definitive findings regarding treatment and suicide are available. Studies examining the costs and benefits of increased monitoring of patients taking antidepressant medications would be valuable.

Whereas the prescription of antidepressants is an empirically supported treatment option for adults, the debate over safety and efficacy in pediatric populations continues. Here, too, an examination of the risks and benefits is imperative (Gunnell & Ashby, 2004; Hegerl, 2006). The present lack of definitive data or guidelines leaves the decision to individual practitioners' clinical judgment and experience. There are two competing concerns, and it is not clear how to balance the risk posed by each. Not treating depression in a child can be dangerous. Antidepressants shorten the duration of the depressive episode, thus reducing the time period during which suicidality is likely to emerge or increase (Hegerl, 2006). Depression left untreated may be more likely to precipitate suicide than the medication itself (Nishawala et al., 2006). On the other hand, data do not definitively rule out the possibility that antidepressant use increases suicide risk. With further research, it may be possible to identify and quantify each of the many risk factors and thereby to make data-based decisions on a patient-by-patient basis. At present, it is impossible to predict accurately whether the potential benefits of antidepressant medication outweigh the potential risks for individual cases. Future research is needed to reduce the unacceptable level of uncertainty plaguing such important decisions.

Given that antidepressants may be helpful to some children with mood disorders, a black box warning was issued rather than a strict ban for prescriptions to youth (Goodman, Murphy, & Lazoritz, 2006; Hammad, et al., 2006). The black box advises that patients be monitored closely when on the medication because antidepressants may cause a rise in suicidal thoughts and behavior, adding that there is no evidence of an increase in suicide risk in those over 24-years-of-age (Food and Drug Administration, 2007). The warning does not implicate antidepressants alone as the cause of suicidality (Goldney, 2006). Despite these caveats, the addition of black box warnings to antidepressants and the subsequent media attention that this received certainly made the public more aware of potential risks, especially for children. Unfortunately, an emphasis on potential risks may overshadow the potential benefits. This may have led to an underprescription of antidepressants, which could leave many children without an effective mode of treatment (Hegerl, 2006). Depression is already undertreated and in the United States, and black box warnings may dissuade depressed patients or parents from discussing the possibility of antidepressant use with their doctors (Druss, Hoff, & Rosenheck, 2000).

Thorough assessments of post-black box prescribing patterns would provide valuable information (Nishawala et al., 2006). Some research along these lines has been conducted. Using a database containing managed care claim information for more than 47 million people, Libby et al. (2007) found a significant decrease in the number of both diagnoses of depression and antidepressant prescriptions in the pediatric population following the issuance of the FDA's warning. Nemeroff et al. (2007) also noted a reduction in the number of youth prescribed antidepressants following the FDA's warning, along with a trend toward psychiatrists, rather than general practitioners, treating depressed youth. It is possible that in light of the FDA's warning, general practitioners are referring patients to specialists for psychiatric attention. In addition, Libby et al. reported an increase of psychotherapy received within 180 days of diagnosis of a depressive episode. It is not clear whether this represents a substitute for treatment with medication, and further research will be needed to explore this possibility.

The blanket warning about potential risks and the

apparent decrease in prescriptions for antidepressants following this warning raise additional concerns. One important factor to consider in treatment planning for suicidal patients is previous repetitious self-harm, as this has been related to a subsequent risk of suicide (Zahl & Hawton, 2004). Does treatment with antidepressant medication attenuate or exacerbate this risk? When offered, prescription in a case of prior self-harm may necessitate closer monitoring during the course of treatment.

Another complicating factor is that non-depressed and depressed patients treated with antidepressants may respond differently to the medication, and agitation and akathisia (restlessness) may be more apparent in non- (or less-) depressed patients treated with antidepressants than severely-depressed patients (Fergusson et al. 2005). Hansen (2001) concluded that a definitive link between akathisia and suicide has yet to be found, but there is still some evidence available in the research literature to support a possible relationship. In one sample, 50% of inpatients who committed suicide displayed severe or extreme agitation in the week prior to the suicide (Busch, Fawcett, & Jacobs, 2003). Inpatients spanned several different primary admitting diagnoses. However, Placidi et al. (2000) compared symptoms of inpatient suicide attempters and non-attempters and found higher levels of agitation in non-attempters. All patients in this sample had a history of at least one depressive episode and met diagnostic criteria for MDD or bipolar disorder. Though the current literature base does not indicate whether increased monitoring actually prevents suicide in these cases, careful monitoring seems prudent until research supports more definitive guidelines. Increased research is also necessary to determine mechanisms connecting antidepressant medication and suicidal behaviors.

Antidepressant medication is not the only treatment available for depression, and as such, other evidence-based treatments should be explored and promoted (Gaudiano & Epstein-Lubow, 2007). In particular, psychotherapy has been shown to be effective in the treatment of depression. For adults and adolescents, efficacious forms of psychotherapy include cognitive, behavioral, and interpersonal psychotherapies (Hollon, Thase, & Markowitz, 2002). Cognitive behavior therapy (CBT), in particular, has shown promise in terms of enduring effects in the treatment of depression (Hollon, Stewart, & Strunk, 2006). de Jonghe, Kool, van Aalst, Dekker, and Peen (2001) found that a brief psychodynamic psychotherapy combined with antidepressant medication outperformed medication alone in the treatment of adult depression, though further studies of psychodynamic psychotherapies would be needed to draw firm conclusions. Reviewing their findings from a meta-analysis, Weisz, McCarty, and Valeri (2006) concluded that psychotherapy is a good alternative to antidepressants in children and adolescents. For example, it might be appropriate to reserve medication for children who do not respond to therapy (Nishawala et al., 2006). Moreover, psychotherapy may be an especially appropriate initial treatment for mildly depressed youth, whereas a combination of psychotherapy and medication may be more suitable for more severely depressed youth (Ebmeier, Donaghey, & Steele, 2006). In TADS, fluoxetine alone, CBT alone, combined fluoxetine and CBT, and clinical management with pill placebo were compared, with the combined medication and psychotherapy condition prevailing in terms of both response and remission (TADS 2004; Kennard et al., 2006). Fluoxetine and CBT performed equally at week 36. Importantly, suicidal ideation decreased more with CBT and combination therapy than in the medication alone condition, and suicidal events were less common in CBT and combination therapy than in medication alone. Thus, there appear to be more risks with fluoxetine alone than psychotherapy alone or combined treatment, making psychotherapy potentially a better choice. Combined treatment had the best performance combined with less suicidality, and furthermore, when pharmacotherapy is combined with psychotherapy, psychotherapy can provide built-in monitoring for suicidality.

If a decision is made to prescribe antidepressants, the doctor has a responsibility to inform the patient and, in the case of a child, the patient's parents (or legal guardians) of potential risks and warning signs of suicidality (Bostwick, 2006). It is important to do so immediately because suicidal behavior is more prevalent early in treatment. Whenever a child is treated with a psychotropic medication, all parties involved (e.g., mental health professionals, patients, and family) should be aware of possible side effects. Those who prescribe antidepressant medication should be trained in evaluation of signs of agitation in youth, as behavioral and psychological side effects manifest differently in children and adults. Under no circumstances should a child be prescribed antidepressants without competent professional supervision. Monitoring should be part of the treatment plan, and for youths this monitoring should be multifaceted to include the patients, the parents, and mental health professionals.

In light of available research, it is debatable whether the issuance of the FDA's black box warning was an appropriate step. It may represent a reasonable precau-

tionary measure that has reduced the risk of suicide, though it may have prevented some patients from receiving helpful treatment and thereby increased the risk of suicide (as well as other negative effects of untreated or suboptimally treated mood or anxiety disorders). Future research is necessary to determine whether the warning should be continued or retracted. The black box warning drew attention to the potentially elevated risk of suicide in youths taking antidepressants, but the consequences of this increased awareness are not yet known. As new data become available, we encourage a careful consideration of all the potential risks and benefits involved in the prescription of antidepressant medications for children and adolescents. Even an apparently reasonable precautionary measure can backfire, doing more harm than good.

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