

**American College of Neuropsychopharmacology**

**EXECUTIVE SUMMARY**

**PRELIMINARY REPORT OF THE  
TASK FORCE ON  
SSRIs AND SUICIDAL BEHAVIOR IN YOUTH**

January 21, 2004



## **American College of Neuropsychopharmacology**

### **EXECUTIVE SUMMARY**

#### **PRELIMINARY REPORT OF THE TASK FORCE ON SSRIs AND SUICIDAL BEHAVIOR IN YOUTH**

This is the Executive Summary of a Task Force report by the American College of Neuropsychopharmacology (ACNP) which evaluated the safety and efficacy of SSRI<sup>1</sup> antidepressants for depressed youth under 18 years. The report was undertaken after regulatory agencies in the United States and United Kingdom voiced concerns in 2003 about the possibility that treatment of depression in children and adolescents with SSRIs may increase the risk of suicidal thinking or suicide attempts. The ACNP Task Force emphasizes that its findings and recommendations are preliminary because it did not have access to all the data held by regulatory agencies and pharmaceutical companies.

#### **The Debate over SSRIs and Suicidal Behavior in Youth**

The U.K. Department of Health, beginning in the summer of 2003, warned doctors against prescribing any SSRI antidepressant drug except fluoxetine for depressed youth under 18 years of age. On the basis of clinical trial results, the agency had concerns that SSRIs, with the exception of fluoxetine (Prozac<sup>®</sup>), were not effective for youth with depression, and may increase the risk of suicidal thinking or suicide attempts.

The U.S. FDA also warned against the use of one SSRI, paroxetine, but stopped short of warning against use of other SSRIs in youth. It later announced that it was conducting a thorough investigation of eight antidepressants, including all currently approved SSRIs. The FDA said that the evidence it had reviewed so far was insufficient to determine whether or not a link exists between SSRIs and suicidal behavior in youth. Instead, the FDA advised physicians to monitor children and adolescents for changes in their clinical state and for increased suicidal risk. FDA said it planned to hold a public hearing on February 2, 2004.

The debate over SSRIs use in youth actually began more than 10 years ago with case reports in the medical literature describing a small number of individuals (primarily adults) whose suicidal tendencies worsened during SSRI treatment, and, in some cases, appeared to improve after stopping the SSRI.

#### **First ACNP Task Force Convenes in 1993**

Responding to the early case reports, the ACNP convened its first Task Force to study the matter in 1993. After carefully evaluating the evidence, the Task Force concluded that there was no scientific evidence indicating that SSRIs could trigger suicidal behavior. Nevertheless, as a matter of prudence, the Task Force advised clinicians caring for suicidal patients to remain vigilant for a worsening of their patients' condition, whether due to illness (most commonly depression), or whether due to the side effects of SSRIs. The Task Force also

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<sup>1</sup> Selective Serotonin Reuptake Inhibitors (SSRI)

recommended more research into the safety and efficacy of antidepressants in depressed and suicidal patients.

### **New ACNP Task Force Convenes in September 2003**

ACNP took the initiative to appoint a new Task Force in September 2003 soon after announcements by drug regulatory agencies. The Task Force evaluated the evidence of safety and effectiveness of SSRIs in youth, including all evidence published after its 1993 Task Force report. Not only did the new Task Force examine all published clinical trial data in youth, but it also sought and obtained for its review unpublished data from several drug sponsors, and data reported to the U.K. drug regulatory agency.<sup>2</sup> **However, because the Task Force did not have access to a substantial amount of unpublished data, including detailed findings held by drug sponsors, this report is preliminary.**

The members of the Task Force are: Graham Emslie, M.D., J. John Mann, M.D., William Beardslee, M.D., Jan Fawcett, M.D., Andrew Leon, Ph.D., Herbert Meltzer, M.D., Fredrick Goodwin, M.D., David Shaffer, M.D., Karen Wagner M.D. Ph.D, and Neal Ryan, M.D. A list of Task Force members and their academic affiliation is attached, as is disclosure of potential conflicts of interest for each member. The ACNP is a non-profit, professional society with revenues from a variety of sources including membership dues, publication sales, registration fees, and unrestricted educational grants from the pharmaceutical industry. The ACNP Task Force on SSRIs and Suicide was supported solely by the ACNP. There was no financial support from the pharmaceutical industry for this Task Force.

The full version of the ACNP Task Force report will be released in the spring or early summer of 2004.

## **TASK FORCE FINDINGS**

### **Depression in Youth is a Serious Public Health Problem with a Risk of Suicide**

Suicide is the third leading cause of death among 15-24 year olds in the U.S. Depression and other psychiatric disorders are the major causes of suicide. Depression annually occurs in about 10% of youth. Most cases of depression are untreated and undiagnosed. Untreated depression is frequently behind most suicides, according to studies of adults and youth.

Although a suicide death is still rare in youth (less than 1% of youth per year<sup>3</sup>), suicidal thinking or suicide attempts are relatively common. Every year, 19% of teenagers (age 15-19) in the general population think about suicide (known as suicidal ideation) and nearly 9% of teenagers make an actual suicide attempt.

The rates of suicidal thinking and suicide attempts are even more frequent in youth receiving care for depression. Studies find that 35-50% of these youth have made, or will make, a

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<sup>2</sup> The UK Medicines And Healthcare Products Regulatory Agency (MHRA)

<sup>3</sup> 0.008% 12-month incidence in ages 15-19 (Anderson, 2002).

suicide attempt. Between 2 and 8% will actually commit suicide over the course of about a decade.

Considering the frequent occurrence of suicidal behavior in depressed youth (whether in treatment or not), case reports of a small number of youth becoming suicidal while taking SSRIs are expected. The Task Force considered two possible explanations for the case reports. One is that SSRIs fail to relieve the suicidal behavior that is part of the depression. A second possibility is that the SSRIs trigger a novel set of suicidal emotions or behaviors.

The Task Force report examined the evidence regarding the possibility that SSRIs increase the risk for suicidal ideation or attempts, but first asked what are the benefits of SSRIs for depressed youth, and what alternatives are available.

### **Several SSRIs Are Effective for Treating Depression in Youth**

Depression in youth not only is a major cause of death, but also causes tremendous suffering and problems in learning, social relationships, and community activities. Depression, if not properly diagnosed and treated when it first appears, can lead to dropping out of school and lifelong problems in adulthood.

The Task Force reviewed the results of 15 clinical trials on the efficacy of SSRIs and other new antidepressant medications (in therapeutic classes other than SSRIs)<sup>4</sup> for depression in youth. The results of these trials, covering a total of more than 2,000 youth, were reported to drug regulatory agencies. Some, but not all, of the results have been published in medical journals.

Each clinical trial typically was double-blind, randomized and placebo-controlled, meaning that youth were randomly assigned by researchers to receive either the drug or a placebo (an inert pill). Most of the clinical trial findings were published in the last three years.

To complicate matters, the clinical trials often use more than one outcome measure to study a medication's efficacy. Selecting different outcome measures can lead to different interpretations of a study's findings. The UK drug regulators, for example, interpreted findings from several SSRI trials as being a negative study, while the Task Force selected other measures indicating a positive study. A negative study means no difference in efficacy between the drug and the placebo, whereas a positive study means the drug is efficacious in comparison with the placebo. A negative study could mean a treatment does not work, or the placebo response rate is high and an active drug effect cannot be detected, or the patient population as a whole is drug resistant (also known as a failed study).

The Task Force, after reviewing the clinical trials summarized in Table 1, identified five SSRIs or other related new antidepressants as being significantly more effective than placebo in at least one trial each: fluoxetine, sertraline, paroxetine, citalopram, and nefazodone. The latter three drugs (paroxetine, citalopram, and nefazodone) were also found to be no

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<sup>4</sup> SSRIs are fluoxetine, paroxetine, sertraline, and citalopram. Other new types of antidepressants, which are not SSRIs, are nefazodone, venlafaxine, and mirtazepine.

different from placebo in one or more separate clinical trials. Venlafaxine was no better than placebo in two clinical trials. No published data were available for mirtazapine.<sup>5</sup>

Across the positive clinical trials, the degree of efficacy varied, depending on the trial's size and methodology. The largest single clinical trial, of sertraline, pooled data from 376 children and adolescents in the U.S., Canada, India, and other countries. It found that nearly 70% of children and adolescents responded, compared to 60% in the placebo group, a statistically significant difference (Wagner et al, 2003). The difference was even greater in two other large trials of fluoxetine and nefazodone. In those trials nearly half or more of youth responded, compared with somewhat more than a third of those receiving the placebo (Emslie et al, 2002a, 2002b).

Thus, based on published and some unpublished clinical trials, the Task Force believes that there is sufficient evidence to conclude that, overall, SSRIs are effective in treating depression in children and adolescents. There are no convincing differences in efficacy outcome across the clinical trials that cannot be explained by different methods of study.

### **Alternatives Not Effective or Readily Available**

SSRIs are the only antidepressant drugs shown to be effective for treating depression in children and adolescents. Another drug class introduced into the market in the 1960s, the tricyclic antidepressants, is not effective for youth. That was the conclusion of a sophisticated type of study known as a meta-analysis, which pooled results from several clinical trials (Hazell et al, 2002). Further, tricyclic antidepressants have more side effects. Tricyclic antidepressants are therefore not recommended as a first-line treatment for depressed youth.

The only potential alternative to SSRIs in depressed youth is a particular form of psychotherapy known as cognitive behavioral therapy. The problem is that this psychotherapy has only been tested in depressed adolescents, not in children. In the adolescent clinical trials, cognitive behavioral therapy was found to work for most adolescents, but a very sizable percentage—about 40%—did not respond (Brent et al, 1997; Clarke et al, 1999). Another problem is that cognitive behavioral therapy is not readily available in most communities.

### **Weak Evidence Links SSRIs to Suicidal Behavior in Youth**

The possibility that SSRIs may trigger suicidal behavior was first raised over a decade ago in a series of case reports describing a small number of individuals whose suicidality worsened during treatment and then sometimes improved after stopping the SSRI. All except one of those reports (King et al. 1991) were in adults (Teicher et al, 1990; Masand et al, 1991; Rothschild et al, 1991; Creaney et al, 1991; Wirshing et al. 1992; Lane et al, 1998). In a few cases, patients were re-started on the SSRIs and the suicidal behavior re-emerged.

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<sup>5</sup> This paragraph and the remainder of the summary lists the drug's generic names. The brand names (with generic names) are: Prozac (fluoxetine), Paxil (paroxetine), Zoloft (sertraline), Effexor (venlafaxine), Cexela (citalopram), (Remeron) mirtazepine, and Serzone (nefazodone).

In medicine, any report of an individual case, or a series of cases, represents a weak form of evidence. Case reports or case series cannot be used alone to draw conclusions about causation (e.g., IOM, 2003). Physicians and scientists use case reports only to raise questions that can be studied more thoroughly in larger and well-designed controlled clinical trials. Controlled clinical trials offer the best kind of evidence from which to infer whether a drug causes a particular effect.

Other questions about the value of the case reports linking SSRIs to suicidal behavior were raised in a separate analysis published in 1992. The analysis found similar case reports of suicidal behavior with every class of antidepressants, as well as with drugs against psychosis and anxiety (Kapur et al, 1992). The analysis also found no consistent relationship between suicidal behavior and (1) the dose of the drug; (2) the time of onset after starting the medication; or (3) raising the dose. The authors concluded that there was no evidence from these case reports of an effect confined to one pharmacological class of drug, or a clear dose-response relationship. They suggested that the one common feature in these reports was a psychiatric disorder known to carry a risk of suicidality.

The 1992 analysis, combined with further review of the evidence then available, including meta-analyses of controlled clinical studies of three antidepressants, was key to the ACNP Task Force report's 1993 conclusion that there was no scientific evidence indicating that SSRIs could trigger suicidal behavior.

Apart from the case reports, one study examined a UK database of adverse drug reaction reports (Medawar and Herxheimer, 2003). These are reports from professionals or consumers submitted to a drug regulatory agency. On the basis of its analysis, the study recommended restrictions on the use of paroxetine and perhaps other SSRIs. But one problem with the study was that there was no control group (i.e., a comparable number of untreated individuals). Another problem was that the study was conducted after a widely viewed television program that might have encouraged greater reporting of a particular type of side effect and a particular medication.

Even in the absence of proof that SSRIs can trigger suicidal ideation or attempts, some speculate that SSRIs may trigger a mixed mood state of mania and depression, which, in turn, carries a greater risk of suicidal behavior. Whether or not SSRIs have such an effect on mood in youth and adolescents also remains to be proven.

Moreover, the diagnosis of bipolar disorder in youth is difficult for even highly experienced clinicians. This further complicates the question of whether the drugs induce suicidality. For example, up to 75% of adults diagnosed with bipolar disorder report having had significant symptoms in childhood, largely in the form of depressed mood. Predicting which children with symptoms of depression will be the ones who later develop bipolar disorder is not possible. Consequently, it is also impossible to determine which children, as a possible result of taking antidepressants, are at higher risk for suicide attempts. A family history of bipolar disorder might be a clue. But answers will only emerge from clinical trials of mood stabilizers with antidepressant properties, or of mood stabilizers in combination with antidepressants in children and adolescents. Those types of studies are needed to determine whether there are other effective therapeutic alternatives.

## **No Significant Increase in Suicidal Behavior in Clinical Trials of Youth**

In the same clinical trials in youth described earlier, investigators also studied the safety of SSRIs. This part of a clinical trial covers what types of side effects (known as adverse events) occurred during the trial. Table 2 brings together all the data available to the Task Force on these five antidepressants: citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine. There were no data available from clinical trials of mirtazapine and nefazodone.

First, a caveat: across the trials, suicidal behavior was captured in the adverse events reports, but the trials did not set out specifically to determine whether the medications lead to suicidal behavior. As a result, the definition of suicidal behavior as an adverse event was left up to the individual clinicians that saw patients in the trial. Therefore, the definition of suicidal behavior was not uniform across the trials or even within the trials.

What is striking is that in none of the trials, involving more than 2,000 subjects, did a single young patient die by suicide.

Regarding suicidal behavior and ideation, the Task Force found no significant difference between drug and placebo for any of the medications (Table 2). The rate of suicidal behavior and ideation among youth on the antidepressant was not statistically different from youth on a placebo.

When looking at suicide attempts, it is important to distinguish attempts with low lethality versus those with high lethality. The profile of someone who attempts suicide in the context of a mood disorder varies by demographic, clinical and biological factors. For example, suicide and very lethal suicide attempts are more common in men, are planned and are associated with a deficiency in the brain serotonin transmitter system. Low lethality, impulsive attempts are made mostly by women in the setting of an inter-personal conflict and not associated with a serotonin deficiency. Thus, to establish a risk for suicide, the rate of more lethal suicide attempts (such as those requiring significant medical intervention) must be shown to be increased on antidepressants relative to placebo. Low lethality suicide attempts and ideation are poorer indicators of risk for suicide than high lethality attempts. Yet no distinction of type of suicidal behavior has been made in data presented by the UK regulatory agency.

(See URL: <http://medicines.mhra.gov.uk/aboutagency/regframework/csm/csmhome.htm>)

The report of the UK drug regulatory agency often states that the rate of suicidal behavior was higher in the antidepressant medication group. But the slight apparent difference, usually by no more than 2%, was not statistically significant for any SSRI. Furthermore, despite the fact that youth on citalopram showed more improvement on suicide ratings than placebo in two clinical trials, the UK report concluded that citalopram may increase self-harm on the basis of reports of suicidal acts or self injury.

Three clinical trials addressed the suicidal risk of paroxetine, but the sponsor, GlaxoSmithKline, only provided a summary statement that combined results from the three. The results from individual trials were not provided. The results were from nearly 400 patients on paroxetine versus nearly 300 treated with placebo. The statement reported that

3.7% of paroxetine-treated patients versus 2.5% of the placebo group experienced suicidal thinking or suicide attempts, but the difference was not statistically significant.

Although patients considered at high risk for suicide are generally excluded from these trials, suicidal behavior and ideation (i.e., thoughts, gestures) in youth are common. The rates appear to be lower in the clinical trials, by virtue of the exclusion and perhaps the therapeutic benefit of the care and attention delivered during a treatment trial, and do not occur at rates that permit detection of a specific beneficial effect of medication. Reports of adverse events do not systematically assess potential benefits of medications on suicidal thoughts.

In an unpublished study of open treatment with fluoxetine in youth, supported by the National Institute of Mental Health, the first 100 youth were rated for suicidal behavior. Based on a suicide item on a depression rating scale, scores from baseline and outcome were analyzed to evaluate improvement or worsening on this item. Forty seven percent of youth showed improvement in the suicide rating by the end of the 12-week study. Forty nine percent showed no change (in many cases there was no suicidal behavior at the start of the study, so there was no room for improvement.) Only 4% showed a worsening of suicidality (G. Emslie, personal communication). It is important to note that the item assessing suicidality is a single item on a depression scale, and this was not the primary intent of the study.

In studies of adults, which analyzed the single suicidal ideation and behavior item in a depression rating scale, SSRIs were sometimes found to be more effective, and never less effective, than placebo in relieving suicidal ideation and behavior or preventing new or emergent suicidality during acute treatment.

In summary, the available data from clinical trials of young people indicate no significant increase in risk of suicidal behavior in those treated with SSRIs for depression. And there were no completed suicides in any of the trials.

### **Additional Evidence Supports Benefits of SSRIs in Reducing Suicide**

There are two other lines of evidence, from toxicology and epidemiology, suggesting the benefits of SSRIs in lowering suicidal risk. Those lines of evidence support one of the fluoxetine clinical trials, described above, which also found a benefit.

### ***Toxicology Studies in Autopsies***

One way to determine whether SSRIs trigger suicide is through toxicological analysis of individuals dying from suicide. In a study of more than 5000 adult suicides, one research team found that most victims had not taken an antidepressant (most commonly SSRIs or other new generation antidepressants) immediately before their death, even though the majority had been depressed (Isacsson et al, 1997). Only 4% had toxic concentrations of antidepressants, meaning that the drugs were used in an intentional overdose.

In a study of 49 adolescent suicides, a research team in Utah recently reported in an abstract that 24 percent had been prescribed antidepressants, but *none* tested positive for SSRIs at the time of their death (Gray et al, 2003).



These two studies, taken together, suggest that suicide is more likely when depressed individuals do not take their medication, rather than when they take it.

### ***Epidemiology Studies***

Another strong line of evidence supporting a reduction in suicidal risk with SSRIs comes from studies of populations. A distinct reduction in the suicide rate of youth (ages 15-24), averaging about 33%, has occurred across at least 15 countries over the past fourteen years (WHO, 2003). The reduction followed three decades of increases. The greatest reductions were in Australia (52%) and Switzerland (50%), and the lowest was (14%) in Japan. In only three countries did the start of the decline precede the introduction of an SSRI. The reduction was unexpected, and it occurred in countries where quite different methods are used for committing suicide.

The decline in the youth suicide rate from epidemiology studies cannot be explained by a reduction in exposure to drugs and alcohol, for their use—at least in the United States—remained constant during the period of the declining suicide rate. Nor can the decrease be explained by better firearm control, for it has been noted in nations where firearms were only rarely used to commit suicide, and where effective firearm control was implemented (as in Australia), alternative methods took the place of firearms (De Leo et al. 2003).

The decline in youth suicide rates coincides, to a striking extent, with significant increases in the prescription of antidepressants to adolescents, mostly SSRIs (Carlsten et al. 2001; Hall et al. 2003; Isacson 2000; Middleton et al. 2001; Olfson et al. 2002; Rihmer et al. 2000; Rushton and Whitmire 2001; Zito et al. 2003).

Publications drawing attention to the relationship between decreasing youth suicide rates and increasing prescription rates have emerged from three major countries: Sweden (Carlsten et al. 2001), Finland (Ohberg et al. 1998), and the United States (Olfson et al. 2003).

Supporting evidence also comes from a natural experiment in Japan. In that country, the youth suicide rate remained stubbornly high, showing none of the decline in other developed countries. It was not until 1997 that the Japanese government gave approval for the manufacture and importation of SSRIs, which previously had not been permitted. In the following year, youth suicide rates started to decline.

### **No Increases in Suicide Found in Clinical Trials of Adults**

More than 20,000 adults have been studied in clinical trials of SSRIs and other antidepressants. This figure is much higher than the number of youth studied in clinical trials.

A large body of evidence—more than 15 studies—has investigated the safety of SSRIs in adults, largely in clinical trials. The overwhelming majority of the studies have reported no convincing evidence of an increased risk of suicide with SSRIs (see report for citations).

The most important of these studies pooled and then analyzed the evidence from a very large FDA database of clinical trials. The database contained information from more than 20,000 adults studied in randomized controlled trials. Analyses of the database found no relationship between SSRIs and suicidal attempts or actual suicides in adults (Khan et al, 2003, 2002, 2001, 2000).

To further examine the validity of this conclusion, the Task Force undertook its own analysis of whether the database analyses by Khan and co-authors had enough patients, and thus enough statistical power, to detect an increase or decrease in suicidal behavior. The Task Force calculated that the database analyses were very robust: they had the power to detect as little as 2-3% change in rates per drug. This calculation reinforced the Task Force's confidence in the conclusion that SSRIs are not associated with suicide attempts or suicides in adults.

In addition to the evidence from clinical trials, epidemiology studies also have found no instances of increase in suicide or suicidal behavior associated with SSRIs use, and in some instances a decrease of suicidal behavior, in adults (e.g., Zaninelli, R. & Meister, 1997).

### **Summary of Findings:**

Depression in youth is a serious public health problem that carries a risk of suicide. Suicide is the third leading cause of death among 15-24 year-olds in the United States and the leading cause of death in several other countries. Because suicide most commonly occurs in untreated depression, diagnosis and treatment of depression require urgent attention.

The ACNP Task Force thoroughly reviewed published and some new unpublished data to evaluate the benefits and risks of SSRIs and other new generation antidepressants for youth under 18 years of age.

The Task Force found several SSRI trials that showed efficacy in treating depression in youth, while other trials failed to demonstrate efficacy. They noted that differences in drug effectiveness across clinical trials may be from differences in methodology and recommended additional study.

The Task Force also found that the category of antidepressants known as tricyclics were ineffective in youth. Other forms of treatment were found to be not widely available to youth, or insufficient data was available to support their effectiveness.

The Task Force concluded that taking SSRIs or other new generation antidepressant drugs do not increase the risk of suicidal thinking or suicide attempts. Three strong lines of evidence in youth—from clinical trials, epidemiology, and autopsy studies—led to this conclusion.

First, clinical trials of more than 2,000 youth found that there were no statistically significant increases in suicidal behavior and suicidal thinking. Most strikingly, there were no suicide deaths in any of the trials. Further, clinical trials of more than 20,000 adults also find that

SSRIs are not linked to suicide. Although no convincing evidence supports a link, the Task Force plans to conduct further analyses in the forthcoming final version of its report.

Second, epidemiology studies from several countries suggest that increased use of SSRIs and other antidepressant drugs *lowers* the risk of suicide. The rate of youth suicide in 15 countries has declined by an average of 33% over the past fifteen years. This period of time has coincided with increases in prescribing of SSRIs.

Third, autopsy studies suggest that suicide is more likely when depressed individuals do not take their medication, rather than when they take it.

The evidence from case reports linking SSRIs to suicidal behavior is weak. The most likely explanation for cases of suicide or attempted suicide while taking SSRIs is that the underlying depression is responsible, not the SSRIs.

The Task Force, after reviewing the evidence as a whole, concluded that the benefits of SSRIs for treating depression in youth outweigh the risks of suicidal thinking or suicide attempts.

The Task Force emphasizes that its findings and recommendations are preliminary. While ACNP reviewed all published data and some unpublished data, it does not have access to a substantial amount of data available to the FDA or to pharmaceutical companies.

## **Recommendations**

The seriousness of depression and suicide in youth underscores the importance of available treatments and of the need to stimulate research and analysis by academic researchers, drug sponsors, and drug regulatory agencies to identify the most effective and safest treatments for depression in youth.

The Task Force makes the following recommendations:

1. The Task Force recommends continued use of SSRIs and other new generation antidepressants as an effective and readily available treatment against depression in youth. It also urges clinicians to ask depressed patients about suicide, suicidal thinking, and plans for suicide.
2. The Task Force urges that all data held by FDA or pharmaceutical companies should be made rapidly available to allow ACNP and other research organizations to conduct an independent evaluation of the risks and benefits of SSRIs in youth and adults with depression and other mood disorders. The data forming the basis of drug approval decisions that are in the public domain and obtainable under the Freedom of Information Act should be placed on a readily accessible website.
3. More attention is needed to: 1) find better measures and systematic assessment procedures for evaluating suicidal behavior in clinical trials; 2) include subjects with suicide risk in clinical treatment trials or developing treatment trials specifically for suicidal children and adolescents; and 3) evaluate other risk factors associated with suicidal behavior (i.e., past suicide attempt).
4. Clinical trials need to be designed in a more uniform and consistent manner. Areas needing more attention include outcome measures, length of treatment, and dosing. For example, rather than doing two fixed-dose, placebo-controlled trials where the optimal dose in this age group is uncertain, resources would be better utilized by conducting a dose-finding study prior to a fixed-dose, placebo-controlled trial.
5. The FDA's plan to pool the data from all antidepressant trials (both in depressed and anxious populations) is highly important. A large data set will allow a variety of variables to be controlled for, such as previous history of a suicide attempt and dosing. This data set should be made available to academic organizations, such as the ACNP, for independent analysis.
6. Some methodological issues in risk assessment need to be addressed at a regulatory level.
  - 1). Actual "suicidal events" in the studies reviewed here are poorly defined. Attempts were defined by the treating clinician at the site, and therefore varied not only across studies, but across sites within a study. Therefore, as recommended by the FDA, a blind re-evaluation of each suicidal event based on case reports is needed.
  - 2) Events that occur up to one month after medication has ceased need to be treated differently in any analysis.
  - 3) Systematic inquiry should be required of past and current suicidal behavior and ideation in any randomized controlled trial being submitted to the FDA of youth or adult depression, regardless of treatment agent. A past suicide attempt is the best-known predictor of future suicide or suicide attempts and potential stratification effects need to

be considered. 4) For both randomized clinical trials, as well as for adverse events during a trial, and adverse event reporting post marketing, a control population is essential in order to draw any meaningful conclusions, given the high rates of suicidal behavior and ideation particularly in adolescents. An emphasis should be placed on monitoring rates of more lethal suicide attempts as a better guide to the risk of suicide.

7. More effective treatments are needed urgently. Randomized controlled trials should not routinely exclude all currently suicidal patients. Additional trials should be conducted in high risk patients, such as those with a history of suicidal behavior, such as the type of study currently funded by the NIMH in bipolar disorder and the recently published clozapine versus olanzapine study. Fears of litigation discourage the development of urgently needed treatments. Ongoing and potential future investigations of the pharmacological treatment of depression and youth may not be ethically feasible if governmental regulatory agencies prematurely judge these compounds to be ineffective and/or dangerous and eliminate the possibility of an erroneous judgment being discovered and reversed.

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**Table 1: Efficacy of Antidepressants for Treating Pediatric Major Depressive Disorder**

<b>Medication</b>	<b>Open / Double-Blind</b>	<b>Duration (weeks)</b>	<b>Participant Ages</b>	<b>Number Of Study Participants (drug &amp; placebo)</b>	<b>Continuous Response:</b> Difference between drug and placebo in the amount of improvement of depressive symptoms (drug vs placebo)**	<b>Categorical Response:</b> Much or Very Much improved on the scale of Clinical Global Improvement (drug vs. placebo)*	<b>Reference</b>
<b>SSRIs (Selective Serotonin Reuptake Inhibitors)</b>							
Fluoxetine	DB	8	8-18	96 (48 fluoxetine, 48 placebo)	58% vs. 32% (p=.013)***	56% vs. 33% (p=.02)	Emslie et al., 1997
Fluoxetine	DB	9	8-17	419 (209 flx, 210 pb)	65% vs. 53% (p=.09)***	52% vs. 37% (p=.03)	Emslie et al., 2002
Paroxetine	DB	8	12-18	275 (93 par, 95 imp, 87 pb)	63% vs. 50% vs. 46% (p=.02)****	66% vs. 52% vs. 48% (p=.02)	Keller et al., 2001
Paroxetine	DB	12	13-18	286 (187 par, 99 pb)	61% vs. 58% (NS) UK: 75% vs. 71% (NS)*****	NS	Milin et al., 1999; GSK, Final Clinical Report (Study 377)
Paroxetine	DB	8	7-17	203 101 par, 102 pb	Change from baseline (p=.68; NS)**	49% vs. 46% (NS)	GSK, Final Clinical Report (Study 701)
Citalopram	DB	8	7-17	174 (89 cit, 85 pb)	Change from baseline (p=.038)**	NS	Wagner et al., 2001
Citalopram	DB	12	13-18	244 (124 cit, 120 pb)	NS	Data unavailable	UK report

(continued on next page)

**Table 1 (continued): Efficacy of Antidepressants for Treating Pediatric Major Depressive Disorder**

Sertraline (2 studies)	DB	10	6-17	376 189 sert, 187 pb	69% vs. 59% (p=.05)***	63% vs. 53% (p=.05)	Wagner et al., 2003
<b><i>Other New Generation Antidepressants (non-SSRI)</i></b>							
Mirtazapine (2 studies)	DB	8	7-17	250 (165 mirt, 85 pb)	Data unavailable	Data unavailable	
Nefazodone	DB	8	12-17	195 (99 nef, 96 pb)	Change from baseline (p=.055; NS)**	62% vs. 42% (P=.005)	Emslie et al., 2002
Nefazodone	DB	Data NA	7-17	Data Unavailable	Data unavailable	Data unavailable	Emslie et al., 2002
Venlafaxine	DB	8	8-17	161	(NS)	(NS)	Physician letter; Executive summary section
Venlafaxine	DB	8	8-17	193	(NS)	(NS)	Physician letter; Executive summary section

\* Categorical response was defined in all cases as a Clinical Global Improvement of depression of “much” or “very much improved.”

\*\* Continuous response: Difference between drug and placebo in the amount of improvement of depressive symptoms (based on Children’s Depression Rating Scale – Revised {CDRS-R}).

\*\*\* Continuous response: Rates of response based on a percent improvement on a depression rating scale (CDRS-R; 30% on fluoxetine trials; 40% on sertraline trials).

\*\*\*\* Continuous response: Rates of response based on minimal symptoms of depression (Hamilton Depression Rating Scale =8).

\*\*\*\*\* Continuous response: Rates of response based on a percent improvement on a depression rating scale (Montgomery Asperg Depression Rating Scale {MADRS}; =50% improvement).

**Table 2. Rates of suicide deaths and suicidal behavior or ideation in clinical trials of children and adolescents with Major Depressive Disorder**

Medication	Total Number** of Youth in Trials	Number of Suicide Deaths	Percent of youth with suicidal behavior or ideation		P Value	Statistical Significance
			<u>Antidepressant*</u>	<u>Placebo*</u>		
Citalopram	418	0	8.9% (19)	7.3% (15)	0.5	Not significant
Fluoxetine	458	0	3.6% (9)	3.8% (8)	0.9	Not significant
Paroxetine	669	0	3.7% (14)	2.5% (7)	0.4	Not significant
Sertraline	376	0	2.7% (5)	1.1% (2)	0.3	Not significant
Venlafaxine	334	0	2% (NA)	0%	0.25	Not significant

\*Number inside parenthesis is actual number of youth

NA=Not available

\*\*Total number of youth given antidepressant and placebo

Sources: Data from published clinical trials, unpublished clinical trials provided to ACNP by drug sponsor, and clinical trial data compiled by the UK drug regulatory agency (MHRA).

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