CME

Antidepressants and Suicide: Putting the Risk in Perspective

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According to the Centers for Disease Control and Prevention (CDC)[1] (2007), more than 30,000 people in the United States died by suicide in 2001, more than 116,000 people were treated and released from emergency rooms after suicide attempts in 2002, and

CME EDUCATIONAL OBJECTIVES

1. Assess the rationale for the current Food and Drug Administration warning that antidepressant medications are associated with an increased risk of suicidal symptoms in children, adolescents, and young adults.
2. Describe some of the problems with assessing suicide risk from randomized placebo-controlled antidepressant medication trials.
3. Discuss relevant findings from larger population-based studies on antidepressant usage and the relative risks of suicide in real-world settings.

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more than 130,000 people were hospitalized following suicide attempts in 2002. Although suicidal thoughts are a symptom of depression, and completed suicide is a tragic complication of depressive illness, in October 2004, the U.S. Food and Drug Administration (FDA) ordered that all antidepressant medications carry a warning indicating that they are associated with an increased risk of suicidal thinking, feeling, and behavior in children and adolescents. In May 2007, the FDA expanded this warning to include information about an increased risk of suicidal symptoms in young adults ages 18 to 24.

These warnings have received much attention in the general media and have caused much controversy and debate about the relative safety of these commonly used drugs and the appropriateness of their use, especially in younger patients. In this article, I will discuss this issue with the goal of putting the risk in perspective.

WHY DID THE FDA ORDER THESE WARNINGS?

Despite the relative effectiveness of antidepressant medications, there has been some concern that these drugs might have a paradoxical effect in inducing suicidal states, at least in a minority of treated patients.[2,3] With the increasing popularity and widespread use of these drugs during the 1990s, such safety concerns became more pronounced and sometimes highly publicized, especially regarding the use of these agents for younger patients.[4]

The availability of complete databases of published and unpublished placebo-controlled randomized clinical trials (RCTs) of antidepressant drugs provides one way to systematically examine this issue. In a review and meta-analysis of 24 RCTs assessing the use of antidepressant agents among more than 4,400 children and adolescents, the FDA concluded there was an increased risk for suicidal behavior or suicidal ideation in approximately 4% of patients taking active antidepressant medications, compared with 2% taking placebo.[5] Although there were no completed suicides in any of these studies, this analysis led to the FDA's original warning in 2004.

The FDA's more recent, expanded warning was based on additional meta-analyses of data that included nearly 100,000 adults 18 and years and older who were enrolled in 372 RCTs conducted during the past 2 decades.[6] No increased risk of suicidal behavior or ideation was detected with the use of antidepressant agents when the analyses were pooled across all adult age groups, but there was a nonstatistically significant elevated risk for patients ages 18 to 24 compared with patients older than 24. Notably, there were only eight completed suicides among all patients (five of 39,729 taking investigational antidepressant agents, one of 10,489 taking an active comparator antidepressant agent, and two of 27,164 taking placebo).

PROBLEMS WITH ASSESSING SUICIDE RISK FROM RCTS

There are several issues that should be kept in mind when examining these data and thinking about the relative safety of antidepressant agents when they are used in general clinical practice.[7] First, these studies are all short-term (typically 6 to 8 weeks and all less than 12 weeks). The majority of patients with depression have a chronic or recurrent course of illness. As a result, treatment ordinarily extends for a longer, often indefinite, period of time. Therefore, the risk of suicide, whether attributable to the illness or to the treatment, must be viewed from a long-term perspective and not just a short-term one. In particular, even if these data do validly identify a modest short-term safety risk, they do not address whether there are increased or decreased risks with longer-term use. In other words, it is not known whether the presence or absence of increased suicidality during short-term treatment has any predictive value with respect to longer-term risk or risk reduction.

Kessler et al[8], for example, compared data from the 1990-1992 National Comorbidity Survey and the 2001-2003 National Comorbidity Survey Replication. Their survey of individuals in the community included questions about the occurrence of suicidal ideation, plans, gestures, attempts, and treatment during the past year. Notably, they found that despite a dramatic increase in treatment, there was no overall significant change in the percentage of individuals with suicidal thoughts, plans, gestures, or attempts during the 1990s. However, when the researchers looked at the prevalence of suicide gestures among people with suicide plans, this rate decreased significantly over time. They also found that treatment increased dramatically among people with suicide ideation who made a suicide gesture and among people with suicide ideation who made an attempt.

A second related problem with these short-term studies is that they provide no data about when the risk occurs or when it might be greatest. Is it during the first few days, first few weeks, or for the entire duration of the study? Given this uncertainty, it is not known how frequently patients should be monitored (whether in person or by telephone) in actual clinical practice and for how long any heightened clinical monitoring should be maintained.

A third problem is that patients in RCTs are not representative of all patients in the "real world" who will take antidepressant agents. On one hand, the FDA-reviewed data are reassuring: There was no increased risk in older adults (who have the highest risk of suicide), a nonsignificant elevation in younger adults, only a 2% difference in risk compared with placebo in pediatric patients, and very few completed suicides overall. On the other hand, patients enrolled in RCTs are generally considered at low risk for suicide. Typically, they are less severely ill, have less complicated illnesses, and have fewer acute risk factors for suicide. Therefore, a small risk for antidepressant-

associated suicide in such a "refined," low-risk patient population might be magnified when the medications are used in real-world patients who have more suicide risk factors.

Tiihonen et al[9] conducted a cohort study of all participants without psychosis who were hospitalized because of a suicide attempt in Finland from 1997 to 2003 and were followed for up to 4 years through a nationwide computerized database. These kinds of patients ordinarily would not be enrolled in an RCT. Curiously, the researchers found that among suicidal participants who had ever used antidepressant agents, the current use of any antidepressant agent was associated with an increased risk of attempted suicide but with a markedly decreased risk of completed suicide and death, when compared with no current use of antidepressant medication.

Finally, these RCTs were designed primarily to assess short-term effectiveness and not specifically for investigating suicide risk. Data on suicidal symptoms that were analyzed by the FDA were collected via adverse-event reports. Although data from adverse-event reports are not invalid per se, they are subject to possible bias[10] that may result in underreporting or overreporting of adverse events. This may be especially important for assessing symptoms as adverse events, which could also be assessed as part of the illness. For example, sexual dysfunction, insomnia, and suicidal thinking can be part of the syndrome of depression, and they may wax and wane during the natural course of illness. For a patient enrolled in an RCT, whether these symptoms, or changes in these symptoms, are reported as adverse events may arbitrarily depend on clinical judgment or may be subject to study-specific rules for determining causality. As such, the FDA-reviewed data findings cannot be dismissed, but they should perhaps be more appropriately viewed scientifically as a retrospective finding that deserves further investigation in a prospectively designed study using specific measures and methods for assessing suicidality.[7] One example of this was the design of the study investigating and comparing the potential for clozapine (Clozaril) and olanzapine (Zyprexa) to reduce suicidal behaviors in patients with schizophrenia or schizoaffective disorder who were at high risk for suicide.[11] The results of this study led to the FDA-approved labeling that clozapine is indicated to reduce the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder.

Findings [from short-term RCTs] should be balanced against the findings from larger populations with widespread exposure to these agents.

DEPRESSION, ANTIDEPRESSANTS, AND THE RISK OF SUICIDE IN THE REAL WORLD

Findings regarding the efficacy and safety of marketed drugs are commonly based on the experience of several thousand patients who have been treated in RCTs.[12] Rare adverse events can therefore easily escape detection among such a relatively small population sample, especially if the inclusion/exclusion criteria are biased against enrolling participants at low risk of such rare adverse events. In addition, adverse events may result from unforeseen interactions with coexisting clinical conditions or other drugs, either of which often exclude patients from enrollment in RCTs. Therefore, the complete safety profile of a drug may not been readily apparent until it is used in real-world practice for several years and until millions of patients are exposed to the drug. Up to half of drugs that are marketed have serious adverse effects that are detected only after approval and widespread use.[13] Experience with the use of antidepressant drugs and the risk of suicide in the real world complements and extends the findings from RCTs.

Since the introduction of the selective serotonin reuptake inhibitor (SSRI) fluoxetine (Prozac) in 1988, overall antidepressant medication use has grown steadily. They have become among the most widely prescribed drugs in the United States and around the world. For example, 15.3 million people purchased 88.3 million antidepressant prescriptions in the United States in 1997.[14] By 2004, these numbers increased to 24.8 million people and 161.2 million prescriptions.

Recently, McKeown, Cuffe, and Schulz[15] examined suicide rates among different age groups in the United States from 1970 to 2002. The study found that adolescents and young adults (ages 15 to 24) showed a continuously increasing trend in rates until 1994, at which point the rates began to decline steadily until 2002. Rates among the oldest group (age 65 and older), which has the highest risk of suicide overall,[1] fluctuated during the 1970s, reached a low point in 1981, increased sharply until 1987, declined steadily through 2001, and then increased somewhat in 2002. Rates among the 45-to-64 age group declined sharply during the late 1970s and more gradually thereafter, but rates increased each year from 1999 to 2002. Rates among the 25-to-44 age group, however, showed a slight increase during the 1970s, relatively stable rates through the 1980s and early 1990s, and a slight decrease after 1995 to fairly stable rates from 1999 to 2002. The decline in suicide rates for the youngest and oldest age groups from 1990 to 2002 was statistically significant. In light of the increased and widespread use of antidepressant medications during this era, these findings are notable, especially given the high risk of suicide among older adults[1] and the increased suicide risk among younger patients reported by the FDA.[5]

To study more closely the relationship between antidepressant prescription rates and rate of early adolescent suicide in the United States, Gibbons et al[16] examined national county-by-county suicide rate data and SSRI antidepressant prescription rate data. They found that counties with higher SSRI prescription rates had lower suicide rates in children and adolescents ages 5 to 14. These results are in agreement with other studies showing a decline in suicide attempts and suicide in adults and adolescents prescribed antidepressant agents.[16-18] The findings from these U.S. studies are also consistent with adult national population studies in other countries reporting that a decrease in suicide rate correlated with increased antidepressant use over time.[19-21]

Although these kinds of studies cannot definitively establish a causal relationship between antidepressant use and suicidality, they clearly demonstrate that there has not been a surge of suicides that might be detected from the widespread use of antidepressant agents in the general population.[12,13] Unfortunately, adverse publicity about the safety of antidepressant drugs and the FDA's initial warning in October 2004 has been associated with a significant decrease in their use among children and adolescents since 2003.[22] Given the relatively favorable risk-benefit ratio of antidepressant agents in pediatric patients,[23] the clinical consequences of this change are as yet unknown, but it is worrisome to note that preliminary data from the CDC found a slight increase in the suicide rate among adolescents in 2004.[6]

CONCLUSION

Concerns about antidepressant drugs will influence patient adherence to treatment.[24] Recent warnings about the risk of suicide associated with antidepressant agents, especially in younger patients, were based on short-term RCTs. These findings should be balanced against the findings from larger populations with widespread exposure to these agents. Nurses should be familiar with the findings from these studies so they can better educate patients and families about the relative risks and benefits of antidepressant medications.[23]

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