LOST IN THE BLACK BOX: JUVENILE DEPRESSION, SUICIDE, AND THE FDA'S BLACK BOX

[Q2] NANCY RAPPAPORT, MD, JEFFERSON B. PRINCE, MD, AND JEFF Q. BOSTIC, MD

Pediatric mental health concerns, particularly depression, continue to be the emerging "new morbidity" for primary care since first reported in 1975.[1,2] The Surgeon General's Report indicates that 1 in 5 of U.S. children suffer a mental illness at any given time,[3] yet 80% of affected children never receive appropriate treatment.[4] Worse, more than 70% of juveniles with significant mood disorders remain undiagnosed and/or undertreated.[5] Poor mental health funding perpetuates inadequate support in schools and in the mental health and juvenile justice systems, which, coupled with an inadequate supply of child psychiatrists, forces pediatricians to provide much of the mental health treatment for children delivered in the United States. Yet only 1 in 10 pediatricians feels prepared to treat depression in children.[6] Here we focus on the epidemiology of depression in youth and on the factors surrounding the recent Federal Drug Agency's (FDA) "black box warning."

EPIDEMIOLOGY OF JUVENILE DEPRESSION

The lifetime prevalence of major depressive disorder in children and adolescents is between 0.4% and 8.3%, with a point prevalence of dysthmia between 1.6% and 8%.[7] The National Longitudinal Study of Adolescent Health Survey identified 9% of adolescents in primary care practices with moderate to severe depressive symptoms, and almost 30% of American high school students sometimes feel so sad or hopeless that they stop doing usual activities.[8] Vulnerability to depression is greater in females (after puberty), and in both females and males with school suspensions, weak family relationships, poor health, or increased health care utilization.

EPIDEMIOLOGY OF SUICIDE

Suicide is always a devastating loss for family, friends, and the community. Suicide remains the third-leading cause of death in teenagers. Within the past year, 16.9% of U.S. adolescents reported seriously considering attempting suicide, 16.5% made a suicide plan, 8.5% attempted suicide, and 2.9% required medical attention for an injury or overdose from a suicide attempt.[8] The most important risk factor for suicide remains depression, but stressful life events, substance use/abuse, irritability, agitation, and impulsivity also increase the likelihood of completed suicide.[9] Completed suicides remain highest in adolescent boys with a history of previous attempts, associated mood disorders or conduct disturbance, and substance abuse.[9]

The American Academy of Pediatrics and the American Psychiatric Association have jointly published practice guidelines for assessing patients with suicidal behaviors.[10] These guidelines encourage clinicians to inquire about self-harming thoughts, plans, and behaviors; reasons for living; and recognition of acute stressors and vulnerabilities, including conflicts with peers and adults, victimization by bullying, or fears of criticism because of sexual preferences. These guidelines focus on identifying and addressing modifiable risk factors, such as treating depression/anxiety, storing guns safely, and treating substance abuse.

ANTIDEPRESSANT MEDICATIONS, SUICIDALITY, THE FDA, AND THE "BLACK BOX WARNING"

The 1997 FDA Modernization Act provided a 6-month patent extension to pharmaceutical companies investigating potential indications of their medications for the pediatric population. Many pharmaceutical companies paid for these studies, so they retained control over the data, including the presentation or publication of any findings. Legislative reform efforts are now underway to change this practice. Pharmaceutical companies often investigate potential indications for compounds, but sometimes doses or other variables emerge as relevant for different disorders, necessitating requiring subsequent trials to determine efficacy. These failed trials may dissuade pharmaceutical companies to pursue an FDA indication.

The inability to gain access to these data has led to perceptions of betrayal by some clinicians and the public after concerns arose about the association between selective serotonin reuptake inhibitors (SSRIs) and suicidality (new onset or worsening of suicidal thoughts and/or new onset or increased suicidal behavior). The SSRI–suicidality link was first proposed in 2002, when the British Medicines and Healthcare Products Regulatory Agency (MHRA) issued a warning about "emotional lability" in adolescents treated with paroxetine.[11] The British warning did not mention any completed suicides, but did suggest that emotional lability appeared to lead to suicidal ideation. The MHRA ultimately "contraindicated" the use of antidepressants, except fluoxetine, in pediatric populations.[11] The *Medical Letter*, a non–industry-sponsored publication devoted to a discussion of all therapeutic agents, responded to this action in 2003, stating that "there are no convincing data showing that SSRIs, including paroxetine, are any less safe in children than in adults," and that "these drugs are much more likely to prevent suicide than to cause it."[12]

Soon after the MHRA expressed its concerns, the FDA launched its own investigation. Examining pooled data from 24 studies on the use of SSRIs to treat depression or anxiety disorders in a total of 4400 children and adolescents, the FDA identified an increased risk of suicidality by a factor of 1.8.[13] When these studies were all pooled, the reported suicidal occurrence was 3.8% in the patients on SSRIs compared with 2.1% in those on placebo.[14] No subjects completed suicide during the course of any of these trials. As a result of safety concerns, the FDA voted 15 to 8 to issue a "Black

Reprint requests: Dr. Nancy Rappaport, 6 Wyman Road, Cambridge, MA 02138. E-mail: nrappaport@comcast.net. (*J Pediatr 2005;■■■:■■■-■■■*)

Box Warning" (FDA Hearing, p. 395), the strongest advisory that the FDA can issue for a medication while still allowing its use. The language of the advisory was altered on February 9, 2005, clarifying that the use of SSRIs is associated with an increased risk of suicidal ideation and behaviors, but a causal relationship between SSRI use and suicidality has not been detected. The FDA added that this conclusion was based on short-term studies.

Significant limitations constrained the FDA in evaluating this suicide data in juvenile patients treated with SSRIs:

1. The FDA performed post hoc analyses, because none of the original 24 studies was designed to evaluate the impact of antidepressant therapy on suicidality. An expert panel organized by the FDA relied on available chart data to best determine whether an event recorded years earlier may have reflected suicidal intent. This analysis represented a retrospective review of past events described in varying detail in varying studies.
2. Relatively few suicide-related events (in 95 patients) were identified among these 4400 patients.
3. Substantial differences among the studies in terms of identification, assessment, and classification of suicidal intent or related events further limited comparison of the studies.
4. Medication noncompliance may have influenced suicidal thoughts and/or related events and was inadequately monitored. Flexible dosing protocols prevented the examination of dose effects on the emergence of suicidality.
5. Many patients seen in typical clinical practice were excluded from the 24 clinical trials designed to investigate efficacy for particular disorders. Patients with severe psychopathology, comorbid conditions, or significant suicidal risk were excluded from these trials.[15]

Beyond methodological factors limiting the FDA's review, findings from other data raised questions about the conclusion that SSRIs increased suicidality in young people. Actual suicides among adolescents tripled between the 1960s and the late 1980s, but have declined by 30% since the early 1990s, coinciding with the introduction of the SSRIs in the United States.[16,17] If SSRIs play any significant role in this decrease in actual teen suicides, then the MHRA and FDA warnings may dissuade the use of these agents, which possibly could lead to a reversal of this downward trend.

Large database examinations have countered the assertion that increased prescribing of SSRIs has culminated in increased suicidality. Olfson et al[18] studied the changes in antidepressant prescriptions and completed suicide in adolescents between 1990 and 2000 and found an *inverse* relationship between the number of prescriptions written for SSRIs and completed suicides. Areas where more SSRI prescriptions were written were associated with lower suicide rates. Between 1990 and 2000, the overall rate of antidepressant prescriptions increased almost 7-fold, mainly with increased SSRI prescriptions accompanied by reduced tricyclic antidepressant prescriptions. As antidepressant prescriptions increased, reductions in completed suicides were noted in adolescents age 15 to 19, particularly in males and those of lower socioeconomic status. Using claims data from both Medicaid and commercial insurers, Valuck et al[19] identified 24,119 adolescents diagnosed with depression and/or receiving antidepressants. Treatment with an antidepressant, either an SSRI or a non-SSRI, resulted in no statistically significant increase in suicide attempts. Adolescents treated with an antidepressant for more than 180 days were less likely to make a suicide attempt than those treated for less than 55 days. Those adolescents with more severe depression and with younger age at time of diagnosis were observed to have some increased risk of making a suicide attempt.

Interestingly, the FDA chose to "black box" all antidepressants, not just the SSRIs. Many of the review panel experts worried that limiting the warning to SSRIs would lead to increased usage of the older tricyclic antidepressants, medications that have much narrower margins of safety and potentially more significant side effects and that are associated with higher rates of completed suicide.[19]

CONCLUSION

The FDA advisory on SSRIs only illuminates what most of us think. Mental health problems in children and adolescents, particularly depression and specifically suicide, warrant careful attention by clinicians. Fortunately, the incidence of suicide has diminished in recent years, and antidepressants may be making some contribution to this downward trend. Still, recognition of mental illness continues to increase, and pediatricians caring for patients with these problems do not always have the necessary training, support, or access to more appropriate services. SSRIs provide a reasonable, relatively expedient intervention for pediatricians, but they have now come under fire, and no comparable substitute is readily available. Given recent events, pediatricians, families, and patients must take an attitude of cautious scrutiny and weigh the risks and benefits of effective treatment to promote growth and avert the debilitating impact of juvenile depression.

0022-3476/$ - see front matter

10.1016/j.jpeds.2005.08.037

REFERENCES

1. Haggerty RJ, Roghmann KJ, Pless IB. Child health and the community. New York: Wiley; 1975.
2. Hagan J. The new morbidity. Pediatrics 2001;108:1206-10.
3. U.S. Public Health Service. Report of the Surgeon General's Conference on Children's Mental Health: national action agenda. Washington, DC: Department of Health and Human Services; 2000.
4. Kataoka SH, Zhang L, Wells KB. Unmet needs for mental health care among US Children. Am J Psych 2002;1548-55.
5. National Institute of Mental Health. Blueprint for change: research on child and adolescent mental health. Washington, DC: author; 2001.
6. Rushton JL, Clark SJ, Freed GL. Pediatrician and family physician prescription of selective serotonin reuptake inhibitors. Pediatrics 2000;105: 82-7.
7. Garrison CZ, Waller JL, Cuffe SP, McKeown RE, Addy CL, Jackson KL. Incidence of major depressive disorder and dysthymia in young adolescents. J Am Acad Child Adolesc Psychiatry 1997;36:458-65.
8. Grunbaum et al. MMWR 2004;53(SS02):1-96. Available at: www.cdc.gov/mmwr/preview/mmwrhtml/ss5302a1.htm. Accessed. [Q3] [Q4] [Q5]
9. Gould MS, King R, Greenwald S, et al. Psychopathology associated with suicidal ideation and attempts among children and adolescents. J Am Acad Child Adolesc Psychiatry 1998;37:915-23.
10. Available at: http://www.psych.org/psych_pract/treatg/pg/pg_suicidalbehaviors/pdf. Accessed. [Q6]
11. Available at: www.mhra.gov.uk. Accessed. [Q7]
12. Are SSRIs safe for children? Med Lett 2003;1160:53-4.
13. Available at: http://www.fda.gov/cder/drugs/antidepressants/default.htm. Accessed. [Q8]
14. Brent DA. Antidepressants and pediatric depression. N Engl J Med 2004;351:1598-601.
15. Brent DA, Birmaher B. British warnings on SSRIs questioned. J Am Acad Child Adolesc Psych 43:379-80.
16. Anderson RN. Deaths: leading causes for 2000. National Vital Statistics Report 50(16). Hyattsville, MD: National Center for Health Statistics; 2002.
17. World Health Organization. 2003. Available at: http://www.who.int/mental_health/prevention/suicide/country_reports/en/. Accessed. [Q9]
18. Olfson M, Shaffer D, Marcus SC, Greenberg T. Relationship between antidepressant medication treatment and suicide in adolescents. Arch Gen Psychiatry 2003;60:978-82.
19. Valuck R, Libby AM, Sills MR, Giese AA, Allen R. Antidepressant treatment and risk of suicide attempt by adolescents with major depressive disorder. CNS Drugs 2004;18:1119-32.