

Ever-Present Adverse Effects

By Jack M. Gorman, MD

With our emphasis on treatment-refractory depression, one cannot help but think about recent media coverage and regulatory events surrounding antidepressant therapy. The current debate about the safety of antidepressant therapy for children and adolescents stands out in particular.

Recently, a pediatrician attending a symposium at the University of Pennsylvania asked me whether I thought that primary care pediatricians should continue to prescribe antidepressants for children with depression and anxiety disorder. As is now well known, data have emerged suggesting a link between selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and an increase in suicidal ideation involving children and adolescents during clinical trials. It is important to bear in mind that no actual suicides occurred and that some of the "suicidal acts" were far from lethal and, arguably, not suicidal. Nevertheless, overall ~1 in 50 children on active medication—significantly more than those on placebo—had new-onset suicidal ideation or actions. The effect was most noticeable for venlafaxine and paroxetine and least noticeable for fluoxetine. As all of these drugs block the presynaptic reuptake of serotonin, it is not clear if the differences among these medications are real.

Despite the fact that only a small number of children (~2%) develop these problems in clinical studies, any potential adverse event must be taken seriously. What has complicated the picture is the emotional outcry surrounding it. The media has accused the pharmaceutical industry of withholding preliminary data that children taking antidepressants are at risk for suicidal thoughts. Whether or not this is the case remains to be seen, but the suggested remedy of requiring companies to publicly register all their clinical trials so that negative and failed trials are revealed is a most welcome development. Currently, companies generally only publish positive trials, creating the impression that drugs on the market always beat placebo in clinical trials. In fact, nearly half of antidepressant trials fail to show a significant benefit of drug over placebo and it is important for clinicians and the public to understand how to evaluate the data.

More problematic were the vociferous testimonials at two Food and Drug Administration hearings on antidepressant use for children by aggrieved parents who were convinced that medications have harmed their children. In some cases, parents insisted that the antidepressants were the direct cause of their child's suicide. These opponents often shouted down parents of children who had benefited from antidepressants,

as well as scientists attempting to weigh the data and provide evidence-based opinions.

One wonders if a similar hearing would be permitted for parents whose children with cancer had died while taking chemotherapy. Every year, cancer claims the lives of hundreds of children and adolescents in this country, most of whom were treated with powerful medications aimed at arresting the spread of malignancies. In some cases, death may have actually been the result of the treatment rather than the underlying disease. Overwrought parents in such cases may understandably blame the chemotherapy for causing the death of their child, but it is doubtful that such heart-rending accusations would be permitted to influence scientific opinion or an FDA decision.

On the other hand, it seems that most everyone, including sensationalist newspaper reporters, thinks they are experts on the treatment of depression. The fact is that for those 13–19 years of age, suicide is the third leading cause of death (after accident and homicide) and accounts for more deaths among adolescents in the United States than all of the other causes below it in the list added together, including cancer. It is about time that the public realizes depression will kill more children next year than cancer.

And so I answered the pediatrician as follows: I am sure you have patients in your practice with type 1 diabetes. You start them on insulin. You know that a few will become profoundly hypoglycemic and will require rapid dose adjustment. That is what you have been trained to watch out for and to handle. It would never occur to you to forego prescribing insulin, even if there were five black boxes for it in the *Physicians Desk Reference*.¹ Similarly, a very small number of depressed children started on an antidepressant may develop self-destructive thoughts. If you feel prepared to monitor this and to intervene if necessary, you should continue to prescribe antidepressants. If you are uncomfortable with doing so, refer your patient to a child psychiatrist.

What we are learning is that the medications psychiatrists prescribe are potent drugs for the treatment of serious and often life-threatening illnesses. Adverse events are obstacles that all physicians must contend with on a regular basis. We should not ignore them, nor should we overreact when they occur. **CNS**

REFERENCE

1. *Physicians Desk Reference*. 57th ed. Montvale, NJ: Thomson PDR; 2003.

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