Antidepressants: The Risk/Benefit Saga Continues

By Ricki Lewis, PhD [2]

Selective serotonin reuptake inhibitors, SSRIs, Suicidality, Depression, Major depressive disorder, Neonatal abstinence syndrome

The dust hasn't so much settled as been whipped in new directions following the FDA's March 22, 2004, advisory and the October 15, 2004, black-box warning of increased suicidality risk in adolescents and children taking selective serotonin reuptake inhibitors (SSRIs) to treat depression. While various studies challenge the FDA warning and researchers inch closer to understanding serotonin's role in depression, new concerns about the widely used drugs are emerging. In the wake of the 2004 FDA advisory statement, prescriptions for SSRIs for patients under age 18 plummeted. It seems unlikely that a fifth of the 1.5 million youngsters with clinical depression in the United States would suddenly improve, and the plunge in prescriptions is especially stark against the backdrop of steadily growing SSRI use. A study of national databases tracking outpatients in hospitals and doctors' offices from 1995 to 2002 found that the number of visits for those aged 7 through 17 years soared from 1.4 million to 3.2 million; antidepressant use rose from 47% to 52%, while psychotherapy fell from 83% to 68%. About half of all visits resulting in drug prescriptions did not include counseling. But different studies give different results. A 2004 national survey on the drug use and health of 22,825 people from the general population, sponsored by the Substance Abuse and Mental Health Services Administration, found that of those aged 12 to 17 years, 2.2 million (9%) reported depression, but only 40.3% of those were receiving or had received treatment. Clinicians are left pondering the fates of those no longer receiving SSRIs. "This dramatic shift raises the serious question of whether those children and adolescents with depression who are no longer taking these medications are receiving any care at all-or are receiving the most effective care," wrote American Psychiatric Association President Steven S. Sharfstein, MD, and American Academy of Child and Adolescent Psychiatry President Richard Sarles, MD, in a letter to the FDA commissioner. In response, Acting Director of the FDA Division of Psychiatry Products Thomas Laughren, MD, suggested that the data may reflect decreased access to the drugs, or a "more rational prescribing" that better weighs the risks and benefits. But Thomas Insel, MD, director of the National Institute of Mental Health, offered another explanation: "Our best guess is that many people, particularly children and adolescents, who had been on SSRIs are now getting the new atypical antipsychotics. The evidence base for treatment of mood disorders with these drugs in those who respond to SSRIs is zilch." Adverse effects of the antipsychotics are serious, he added. Others fear that the antidepressant-suicidality warning focuses on avoidance, rather than tracking treatment. "Close monitoring is clearly needed, but because treatment is often ineffective, not because it is dangerous. Of every 2000 patients who start antidepressant medications, 1 will die by suicide in the next 6 months and 800 will continue to be severely depressed. Those who do poorly often discontinue medication and don't return for follow-up care," said Greg Simon, MD, MPH, a psychiatrist with the Center for Health Studies, Group Health Cooperative, Seattle. Simon's team reviewed 65,103 persons in a large health plan who were treated with antidepressants between 1992 and 2003. The number of suicide attempts fell by 60% in the month after drug treatment began and continued to fall in the first 6 months. The study also found fewer suicide attempts among patients receiving SSRIs than among patients receiving older antidepressants. The health plan group more accurately mirrors the general population than past studies on inpatients, the researchers claimed. Their study placed the risk of suicide during initial treatment at 1 in 3000 and the risk of a serious suicide attempt as 1 in 1000. However, FDA statements in July and December 2005 claimed that "taking antidepressants may increase suicidal thoughts and actions in about 1 of 50 people 18 years or younger." It appears that suicidality and suicide attempts are not the same end point. A more recent report from the FDA reveals the confusion in terminology. The title of the online version reads "Suicidal Risk in Antidepressant Drug Trials," yet the title of the actual paper is "Suicidality in Pediatric Patients Treated with Antidepressant Drugs." The paper is a meta-analysis, indicating "a modestly increased risk of suicidality" of 1.95 for patients receiving SSRIs. There were no actual suicides in the large study group. Whatever the numbers, many agreed that careful follow-up is critical to successful
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Treatment. The FDA calls for weekly face-to-face meetings between the health care provider and patient or family member for the first 4 weeks, then every other week for the next 4 weeks, and then as needed. Insel agreed. "The problem in terms of the suicide connection for adolescents taking SSRIs is not the medicine, it's the care. Pediatricians write prescriptions and say 'come back in a month.' This is not safe. The risk of suicide is when the person starts to feel better and has more energy. That's when you see impulsive behavior. If you prescribe this medication, you have to follow someone very carefully. Monitor how they respond by seeing them within a week or at least talk to someone in the family. Treating depression requires much closer follow-up than prescribing penicillin to treat a strep throat." The debate over suicidality risk reveals a subtle conundrum-analysis of the effects of antidepressants far exceeds understanding of how they work. This has led to a substantial disconnect between public expectation and what is actually known about SSRI mechanisms (see Box). While many researchers are discovering the steps of serotonin activity at the synapse, discussed below, other studies approach the mechanism question by seeking commonalities among the clinically depressed. Many report on such factors as circumstance, gender, and age, and some confirm the obvious. For example, a comparison of therapy with an SSRI, a tricyclic, and interpersonal psychotherapy found that people with mid to high incomes respond better to treatment and are less likely to have suicidal thoughts than those with low incomes and little education.6 A study of 42,000 twin pairs found a heritability estimate of 42% for women and 29% for men.7 Heritability estimates genetic contribution to variability in a trait in a particular population. Kenneth Kendler, MD, professor of psychiatry and human genetics at Virginia Commonwealth University School of Medicine in Richmond, attributed higher heritability for depression among women to cycling hormones. And the latest antidepressant alarms are sounding from the perinatology corner. PERINATAL PERIL? Ten percent to 15% of women of reproductive age have major depressive disorder (MDD). "Because SSRIs are considered relatively safe, they are widely used during pregnancy and possibly for very mild disease states," said Gil Klinger, MD, an instructor in the Department of Neonatology at Schneider Children's Medical Center of Israel in Petah Tiqwa. But data are beginning to associate SSRI use in pregnancy with multisystem effects on the neonate. That means making tough, individual decisions on drug use, said Insel. "You have to do the math. Are there advantages to the fetus of stopping the medication, versus recurrence of depression?" In December 2005, the FDA and GlaxoSmithKline, the manufacturer of paroxetine (Paxil) commented on interim results of 2 clinical trials that indicate a doubled risk of certain cardiovascular malformations among newborns exposed to the drug in utero. Specifically, the Swedish National Registry found risk, mostly for septal defects, of 2% in exposed infants and 1% for unexposed controls. The second report, using a US insurance claims database, found a 1.5 elevation in risk for cardiovascular defects (again mostly septal) with paroxetine compared with other antidepressants and an overall doubling of risk for all birth defects. In response, the FDA switched the status of the drug from category C to the more restrictive category D. Selected rare defects are also elevated. At the Teratology Society annual meeting in June, investigators from the University of British Columbia reported a 3-fold increase in risk of omphalocele for first-trimester SSRI exposure and double that with paroxetine.8 But Lee S. Cohen, MD, associate professor of psychiatry at Harvard Medical School, emphasized the importance of distinguishing relative from absolute risk in interpreting large-scale studies. "A 6.4-fold increase in risk for omphalocele translates into an absolute risk of only 0.16%, approximately 2 of every 1200 births." Christina D. Chambers, PhD, MPH, assistant professor of pediatrics and family and preventive medicine at the University of California, San Diego (UCSD), School of Medicine, and coworkers linked SSRI exposure to elevated risk of persistent pulmonary hypertension of the newborn (PPHN).9 This condition results when the high pulmonary arterial pressure that limits circulation to the lungs in the fetus persists after birth, sending poorly oxygenated blood into the systemic circulation. The pulmonary arterioles constrict and smooth muscle cells proliferate. PPHN affects 1 to 2 per 1000 newborns, with a 1% to 2% fatality rate, with neurologic problems persisting in about half of the survivors. The UCSD researchers previously discovered that infants exposed to fluoxetine beyond the first trimester had a significantly higher rate of developing a syndrome variously described as "neonatal withdrawal," "neonatal toxicity," and "neonatal adaptation problems."10 The condition "includes everything from jitteriness to hypoglycemia, tachycardia, hypertonia or hypotonia, failure to cry or high-pitched cry, problems with temperature regulation, and seizures," Chambers said. Because 2 of the 73 long-exposed infants had PPHN, the researchers investigated increased risk for this more serious condition. In the 2006 study, they detected 14 cases among offspring of 377 women who had taken SSRIs past the 20th week of pregnancy, compared with 6 cases among 836 controls, indicating a 5- to 6-fold increase in risk. The researchers estimate the risk of PPHN after SSRI exposure during the third trimester is 1 in 100. "The
milder respiratory complications seen with late exposure to SSRIs might be on the continuum that includes PPHN at the more severe end," she added. The association makes physiologic sense. SSRIs accumulate in lung tissue. Serotonin inhibits synthesis of nitric oxide, which is a vasodilator, and stimulates vasoconstriction and division of smooth muscle cells. A study from Klinger's group in Israel supports the increased risk of congenital anomalies and neonatal abstinence syndrome, which includes tremor, GI distress, increased muscle tone, sleep disturbance, and high-pitched cries. The researchers compared the newborns of 60 women who took SSRIs during the third trimester with 60 control infants.11 Of the 60 exposed newborns, 18 had the syndrome. In 8 of these, symptoms were severe, with 3 major congenital anomalies (2 ventral septal defects and 1 hydronephrosis with ureteroceles). None of the control infants had symptoms. However, the neonatal abstinence syndrome resolved within 48 hours. Despite these associations, for many pregnant women, the benefits of SSRIs are justified. "We are not recommending cessation of SSRI treatment during pregnancy because depression during pregnancy has its own risks. However, it should be kept in mind that prolonged SSRI exposure has at least a short-term effect on the newborn," said Klinger. Still, he and others advise using the minimal SSRI dosages possible, avoiding polytherapy, and re-evaluating use of the drugs for mild cases of depression. Lee Cohen and coworkers quantified the risk of discontinuing antidepressant treatment during pregnancy.12 Their study began with 201 women in whom MDD was diagnosed before pregnancy who took antidepressants for at least the first 16 weeks of pregnancy. Several women dropped out, but 82 continued to take the medication, and 21 of them relapsed (26%). Of 65 women who stopped taking the medication while pregnant, 44 (68%) had a relapse of MDD. Half of the relapses occurred during the first trimester and 90% by the end of the second trimester. The only predictors were duration of depression before pregnancy and the number of recurrences. Cohen called studies on SSRI use in pregnancy a "volley of conflicting reports." Some studies are prospective, others retrospective. Some participants are recruited sequentially; others volunteer. Some studies focus on one SSRI; others lump them together. Some emphasize relative risk when absolute risk may be the more practical comparison. Studies have different designs and assess different defects. Cohen advised awaiting the final, peer-reviewed results and conclusions of the ongoing studies that provoked the December 2005 FDA statement about the association between SSRIs and birth defects. MECHANISM Exactly how SSRIs work is more complex than a correction of the circular-reasoning "chemical imbalance." "The serotonin hypothesis is based on the efficacy of SSRIs. That is, that depression has something to do with deficient serotonergic signaling," said Paul Greengard, PhD, Vincent Astor Professor in the Laboratory of Molecular and Cellular Neuroscience at Rockefeller University in New York City. Boosting serotonin levels somehow improves neuron survival and communication. Several research groups are homing in on the ligand-receptor interactions and signal transduction pathways that underlie SSRI action. A prime suspect has been the serotonin transporter that sends serotonin back into the presynaptic cell. Several studies have associated a "short allele" genotype for the transporter with vulnerability to developing depression following trauma. However, positron emission tomography analysis of transporter binding potential in 25 medication-free depressed patients compared with 42 healthy controls showed that although binding in the amygdala and midbrain decreased in depressed patients, this did not correlate with genotype for variation in the promoter of the serotonin transporter gene.13 These results suggest that variations in how a person responds to trauma arise during development and are not inherited. Instead, an early event may set neural connections in a way that later affects mood, and the SSRIs somehow restore the original settings. Furthermore, the distribution of serotonin transporter molecules varies in time and space.14 Rodent experiments indicate that levels peak at birth, supporting the idea that early abnormalities set the stage for later dysfunction. Blocking transporter production in late gestation results in fearful and stressed adult rats. Location also affects serotonin transporter activity, with sometimes antagonistic effects. Blocking transporters on axons in the cerebral cortex and amygdala, for example, increases serotonin levels and signaling at the receptors. However, blocking transporters on cell bodies of the raphe nuclei in the brainstem activates autoreceptors, which inhibits presynaptic release of serotonin, dropping neurotransmitter levels in the synapse. Other candidates for key roles in SSRI action are the 14 known serotonin receptor subtypes. Greengard and colleagues focused on the 5-HT1B receptor subtype, and identified a protein, p11, that transports the receptor to the cell membrane.15 The team analyzed the link between p11 and depression in postmortem human brains and mouse models. "If the mice overexpress p11, they behave as if given an antidepressant drug. But if you knock out p11, you see the opposite effect," Greengard said. Levels of p11 mRNA were higher if mice were given imipramine or electroconvulsive therapy. The team is experimenting with SSRIs, for which timing and dosing are more complex, he added. Although further studies in
depressed patients are needed, the results are encouraging. "Our findings demonstrate that patients with depression and mice that model this disease have decreased levels of p11 protein, and they suggest that drugs that increase p11 are likely to have antidepressant properties," said Per Svenningsson, PhD, team member and research assistant professor at the Karolinska Institute in Stockholm. THE FUTURE Antidepressant studies present many variables. This fact translates into a need for large numbers of participants, with careful tracking of pertinent characteristics. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study may ultimately provide that power, but results from phase 1 are somewhat distressing.16 The STAR*D study is examining 2876 patients from 23 psychiatric facilities and 18 primary care offices, targeting the "real" clinical world. Patients learned about participation at their doctor visits, rather than answering ads or being recruited. Histories were taken, as well as DNA samples for single nucleotide polymorphism analysis. In phase 1, all participants took citalopram (Celexa, Forest Laboratories) because it can be stopped easily, is taken once a day, is relatively safe for the elderly and ill, has few drug interactions, and requires few dose adjustments. Participants had 5 or 6 visits over the first 12- to 14-week treatment period and rated side effects and signs of improvement. The end point was remission. At the end of the 14-week period, about one third of the patients had responded and another 10% to 15% reported some relief. Echoing other studies, responders had better jobs and education, whereas nonresponders were more likely to have substance abuse problems, anxiety, other illnesses, and a poorer quality of life. The 70% of patients who did not respond to citalopram moved on to phase 2 to try a different drug or psychotherapy. The STAR*D trial begins with a broad sampling, but will zero in on which characteristics predict success with which treatments. "Maybe we can predict better response through genotype but maybe not. Maybe having had a family trauma, or something else in the family history, will be more predictive. That is what the study is all about. When all the data are crunched, about 9 months from now, we'll be able to say, 'these people should get this treatment,'" said Insel.17 In the final analysis, the seriousness of depression may counter any risks. Said Insel, "It is a deadly illness. For MDD that requires hospitalization, you're talking about a 4% mortality. There are 30,000 suicides a year, which is nearly twice the number of homicides. Depression is one way to get to a suicidal state. It has the highest disability rate of any medical illness among those aged 15 to 44 in developed countries, and it's very common. We need to think about the importance of treatment." Klaus Ebmeier, professor of psychiatry at the University of Edinburgh, recently reviewed treatments for depression,18 and agreed. "Recent moral panics about suicidal effects and dependence-inducing potential of antidepressants have tilted the balance of publicly perceived risk against them, but both their effectiveness and their ready availability make them the likely choice for most patients." RICKI LEWIS, PhD, a geneticist, textbook author, and freelance writer in Scotia, NY, is a contributing editor for Applied Neurology. REFERENCES 1. Lewis R. Antidepressants and suicidality: how strong a link? App Neurol. 2005;1(1):12-17. 2. Rosack J. New data show declines in antidepressant prescribing. Psychiatr News. 2005;40(17):1. 3. Ma J, Lee KV, Stafford RS. Depression treatment during outpatient visits by U.S. children and adolescents. J Adolesc Health. 2005;37:434-442. 4. Simon GE, Savarino J, Opsenskalski B, Wang PS. Suicide risk during antidepressant treatment. 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