

## **Kids on Meds -- Trouble Ahead**

### **Antidepressants, designed for adults, may be altering the brains of kids who take them**

By Paul Raeburn

On February 7, 2004, the body of Traci Johnson, a 19-year-old college student, was found hanging by a scarf from a shower rod in a drug company laboratory. Johnson had no apparent signs of depression, and the reason she killed herself was a mystery. What made her death different from other such tragedies is that she was a subject in a trial of an experimental antidepressant. The company, Eli Lilly, noted that four other patients given the drug in earlier trials had also committed suicide. Not long afterward, prompted by Johnson's death and others, the Food and Drug Administration warned doctors that antidepressants might increase the risk of suicide in children and adolescents.

Johnson's death and the FDA's warning underscored the difficulty of treating depression in children. Was the cure worse than the disease? Nearly two decades after doctors began giving antidepressants to children, it is a question they still cannot answer definitively.

Graham Emslie, a psychiatrist at the University of Texas Southwestern Medical Center at Dallas, was one of the first psychiatrists to treat kids with antidepressants. His patients—children and teenagers—were in the grip of life-threatening depression. He wanted something more for them than the talk therapy that at the time was the only option.

Prozac and a growing number of similar successors were just then proving to be effective in treating depression in adults. But the drugs had not been tested in the supple young brains of children. Frustrated by the lack of alternatives, Emslie and others began to prescribe them anyway. They hoped the benefit would outweigh the risks—although there was no evidence to support that.

Despite the unknowns, the use of antidepressants in children and teens exploded during the 1990s. According to Julie M. Zito, a researcher at the University of Maryland who has studied antidepressant use in children, about 1.5 million kids younger than 18 are taking the medications in the U.S. (This figure comes from insurance industry and Medicaid data.)

Now, however, research suggests that suicide is only one of the potential risks. Studies have found that Prozac-like drugs might interfere with normal patterns of growth in children's still developing brains. Although the research is not conclusive, it is possible that kids on antidepressants are trading one psychiatric diagnosis for another. Children who take these drugs—in some instances starting in the preschool years—could find short-term relief and then grow up into edgy, anxious, dysfunctional adults.

## Shaping the Wiring?

Amir Raz, a professor of clinical neuroscience in the psychiatry department at McGill University, is one of a handful of researchers raising concerns over the continued use of antidepressants in children and teens. "The human brain is developing exponentially when we are very young," he says. "And exposure to antidepressants may affect or influence the wiring of the brain, especially when it comes to certain elements that have to do with stress, emotion and the regulation of these."

The drugs in question, Prozac and its relatives—including Celexa, Paxil, Zoloft and others—affect brain levels of the neurotransmitter serotonin, which helps to transmit signals between neurons. The drugs are known as selective serotonin reuptake inhibitors, or SSRIs, because they inhibit the removal of serotonin from the synaptic cleft (the space between neurons), leaving more of the transmitter available to exert its effects through neuronal receptors.

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Raz thinks messing with serotonin in kids is a bad idea. In addition to serving as a chemical messenger, serotonin acts as a growth factor during the first years of life. It encourages the formation of connections, or synapses, between neurons, and it is crucial for the acquisition of a normal response to anxiety-producing events in adulthood. It is also found elsewhere in the body, where it performs a variety of other functions. Drugs that alter serotonin during these critical developmental years could alter brain function in unpredictable ways, Raz says.

Not long ago, the orthodox view was that the brain grew rapidly during childhood and that by about age 12 the brain was wired up and ready to go. For better or worse, that was the brain you would rely on for the rest of your life.

"That's still very widely taught in psychology classes in college," says Jay Giedd, a psychiatrist at the National Institute of Mental Health. Giedd is one of the pioneers whose work has demolished that view. What they have found, instead, is that the teenage brain is a work in progress, under-going continuous change and remodeling, at least until the mid-20s—and perhaps longer.

Using the latest brain-scanning technology, Giedd and others have shown that gray matter—made up of nerve cells—undergoes a burst of overproduction just before puberty. During the teenage years, some of that gray matter is pruned away, as the brain discards neurons it does not need. Some neuronal connections are strengthened; others are weakened. A young piano student, for example, might strengthen connections in the auditory part of her brain. Some of those same connections might fall away in the math student, while he toughens up connections in a part of his brain responsible for abstract mathematical thought. It is a neurological use-it-or-lose-it proposition.

This process is not yet well understood. But if the teenage brain is still in flux—reshaping itself in response to outside stimuli—then perhaps bathing it with drugs that affect serotonin—and who knows what else—might be a very bad idea, some researchers say.

### **Born on Prozac**

It is not just a theoretical concern. Evidence to support Raz's viewpoint comes from a study by Jay A. Gingrich, a professor of psychiatry at Columbia University's Sackler Institute for Developmental Psychobiology.

Gingrich used mice that were genetically altered so that they lacked the ability to mop up serotonin. They were—in effect—born on Prozac. He wanted to see how depression was related to serotonin and norepinephrine, another neurotransmitter. "Our simple-minded idea was these mice would look like mice treated chronically with Prozac," Gingrich says. They should have been free of anything like a mouse's version of depression or anxiety.

Gingrich found quite the opposite. Because he could not chat with them about their feelings, he gave the mice stress tests. (An inability to handle stress is one hallmark of depression.) He put a small electric charge on the floor on one side of their cage. Normal mice will quickly learn to escape the tiny shock by running to the other side. These mice did not. "They have a tendency to freeze," he says. "They stay on the same side where the foot shock is being administered, or they escape much more slowly." The mice—?despite having lived their entire lives as if they were on Prozac—were afflicted with what looked suspiciously like an anxiety disorder.

Gingrich concedes that the response of the mice to the stress test "sounds like a long way from depression" in humans. It is a little tough to imagine a depressed mouse—unable to get out of bed in the morning, plagued with doubts and fears, losing interest in cheese and harboring dark thoughts of self-destruction. But mice have brains that are quite similar to ours: We share some of the same serotonin-related genes. And the wiring is much the same. "You can demonstrate changes in their behavior that have some similarity with changes in a human that's depressed," he points out.

Maybe, Gingrich thought, the anxious mice suffered because of the tinkering that had been done to their genes. To find out, he repeated the experiment, this time giving Prozac to normal mice when they were very young. He let them grow into adults and tested their stress response. He published the results of both experiments in 2004. "They really fell apart," Gingrich says. "It was some change in the way their brains were wired. And it occurred because of the Prozac."

Finding these effects in mice is a long way from proving the same thing happens in humans. But the point of such animal studies is to search for potential problems and to raise questions. Gingrich's work certainly raises issues about the safety of antidepressants in children.

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Gingrich is not the only one to raise such matters. Tim Oberlander, a pediatrician at the University of British Columbia in Canada, reported in February 2005 that infants exposed to SSRIs before birth are less sensitive to pain than their counterparts who were not exposed. It is unclear how that finding ties into Gingrich's work, except that it, too, raises suspicions about the effects of SSRIs on the developing brain.

In January 2003 the FDA reported that children who took Prozac for 19 weeks had grown, on average, almost half an inch less—and gained two fewer pounds—than kids who received a dummy pill. "We don't know if this is a temporary effect or will become more accentuated over time," said Thomas Laughren, who heads the FDA's psychiatric drug evaluation, in the journal *Science*. "That's one of the problems with the use of drugs in kids: we don't know the long-term risks."

### **Diagnosis Is Key**

Even in the face of this evidence, however, many psychiatrists believe that antidepressants do far more good than harm in children and teens. Like Emslie in Texas, Harold Koplewicz, a professor of psychiatry at New York University and one of the city's top child psychiatrists, has been using SSRIs aggressively in children and teenagers for more than a decade. "I am probably the first person to give these meds to kids clinically," he says. As recently as a few years ago, most psychiatrists thought they should try talk therapy with kids before giving them medication. But that has changed, he declares.

He has seen what happens to teenagers who are not treated. "After they've had one episode of depression, they're 60 percent more likely to have another. If they have two, they're 90 percent more likely to have a third. And subsequent episodes are more difficult to treat.... Every good clinician will tell you the risk of not taking the medication is greater" than the possible risks of taking SSRIs.

Evidence is emerging to support Koplewicz's position. In an effort to learn exactly how antidepressants work in young patients, David Rosenberg, chief of child and adolescent psychiatry at Wayne State University, is using brain scanners to look at depressed children and adolescents. "We are seeing striking changes in the chemistry of the brain," Rosenberg says. But not the changes that medication critics might expect. His research focuses on the chemical messenger glutamate. "Glutamate is kind of like the brain's light switch," he notes. "If serotonin is the lighting in the room, glutamate would be the switch that turns serotonin on and off."

Rosenberg has found that a reduced level of glutamate in certain parts of the brain is linked to depression. And the effect of antidepressants is clear: after treatment, glutamate becomes normal, and the symptoms of depression diminish. "When prescribed appropriately, antidepressants do far more good than not," he says.

What is more, Rosenberg's brain scans have shown that not using antidepressants in depressed patients might have a lasting influence on the brain as well. He has found that untreated depression eats away at important parts of the brain. "In adults, the longer you have the illness, the less gray matter you have in the amygdala, the hippocampus and the temporal lobe areas," he

says. All those brain regions are associated with thinking and learning. Preliminary results suggest the same is probably true with children and teenagers.

Rosenberg is careful to say that the benefits outweigh the potential for harm only when antidepressants are prescribed appropriately. "Antidepressants can be dangerous if the diagnosis is not accurate," Rosenberg says. "If you don't have a true clinical depression and you're getting antidepressants, probably at best it won't help and at worst it can do a lot of harm."

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That is a particular problem with children, many of whom are misdiagnosed. Depression in teenagers "is a difficult diagnosis, because it seems like adolescence on steroids," Koplewicz says. Adults with depression usually recognize that they have a problem, and they want to fix it. Children and teenagers rarely ask to see a psychiatrist. They have to be cajoled, wheedled or somehow lured into the psychiatrist's office. And getting there is only part of the problem. With the exception of experts such as Koplewicz, psychiatrists—even child specialists—are not very good at diagnosing depression. Family doctors and pediatricians—who prescribe most of the antidepressants—are worse. Often the diagnosis is made by trial and error. Doctors try one drug. If it does not work, they prescribe another, until they find something that does.

The patients of clinicians like Koplewicz and Emslie, who were among the first to receive antidepressants as children, are the best resource of all for scientists who want to study the long-term impacts of antidepressants on kids. If children who started taking SSRIs as toddlers can grow into young adults without major psychological problems, then perhaps all the worrying has been for naught. Emslie has continued to follow some of the patients to whom he first gave antidepressants 15 years ago. The patients have not been examined rigorously, but based on cursory examination, they seem fine. "In terms of anything that's grossly apparent, we haven't seen any evidence of problems in development," he says.

Emslie has not done a formal study of these adult children of Prozac. If the drugs cause subtle but important changes in brain development, he could easily miss them. To be sure that they are healthy, he would need to compare them with controls—similar young adults who had not taken Prozac as children. It is also possible that these patients would be doing much worse now if they had not taken Prozac when they were younger. But again, in the absence of a formal study, it is impossible to know. And it is a difficult issue to try to study: it would be unethical to withhold potentially useful drugs from children who need them or to give them to children who do not.

Emslie believes that the use of antidepressants in still developing young brains might actually prevent the development of hardwiring for depression. "In the really early age people, you might influence the way neurotransmitters develop," he says. And in children, "you might not have the same side effects you see in adults."

Another encouraging piece of news appeared in April, when University of Pittsburgh researchers reviewed 27 studies of antidepressants in children and adolescents and concluded that the benefits far outweigh the risks. The researchers called on the FDA to reconsider its warning on antidepressant use in children and teens.

It could be years before these questions are resolved. In the meantime, Emslie and others will continue to prescribe SSRIs in children—because they are concerned about the alternative. Untreated depression in children is a scourge that afflicts not only them but also their parents, their brothers and sisters, their teachers and their friends. It turns childhood into a dark, interior battle for survival. Psychiatrists are not the only ones arguing for the continued use of antidepressants; many of their patients and the parents of their patients seek the medicines, too. "It seems," Emslie says, "that the impact of depression, the best we can judge it, is greater than the impact of the treatment." Koplewicz agrees. "At this time," he says, "the best treatment for teenagers is Prozac-like drugs."

### **Further Reading**

Early-Life Blockade of the 5-HT Transporter Alters Emotional Behavior in Adult Mice. Mark S. Ansorge, Mingming Zhou, Alena Lira, René Hen and Jay A. Gingrich in *Science*, Vol. 306, pages 879-881; October 2004.

Pain Reactivity in 2-Month-Old Infants after Prenatal and Postnatal Selective Serotonin Reuptake Inhibitor Medication Exposure. Tim F. Oberlander, Ruth Eckstein Grunau, Colleen Fitzgerald, Michael Papsdorf, Dan Rurak and Wayne Riggs in *Pediatrics*, Vol. 115, No. 2, pages 411-425; February 2005.

National Estimates of Antidepressant Medication Use among U.S. Children, 1997-2002. B. Vitiello, S. H. Zuvekas and G. S. Norquist in *Journal of the American Academy of Child and Adolescent Psychiatry*, Vol. 45, No. 3, pages 271-279; March 2006.

Antidepressant Medications for Children and Adolescents: Information for Parents and Caregivers. National Institute of Mental Health. Available at [www.nimh.nih.gov/healthinformation/antidepressant\\_child.cfm](http://www.nimh.nih.gov/healthinformation/antidepressant_child.cfm)

Antidepressant Use in Children, Adolescents, and Adults. Food and Drug Administration. Available at [www.fda.gov/cder/drug/antidepressants/default.htm](http://www.fda.gov/cder/drug/antidepressants/default.htm)