CEI OnPoint

Competitive Enterprise Institute
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Advancing Liberty – From the Economy to Ecology

March 3, 2009 **No. 151**

Black Box Panic

How the FDA's Bad Science Leads to More Teen Suicides

By Jerome Arnett, Jr., M.D. and Gregory Conko*

President Barack Obama has designated overhauling American health care as a priority of his administration, and he has indicated that whomever he appoints to head the U.S. Food and Drug Administration (FDA) must implement "a stricter regulatory structure" and redouble the agency's focus on food and drug safety. With mounting pressure for the incoming FDA Commissioner to dramatically reform the agency, it is worth noting that when regulators are pushed to err on the side of safety, they often make society less safe, not more. A good example is the FDA's recent crackdown on prescription antidepressants, which has led to a drop in their use and a corresponding increase in suicides among teenagers and young adults.

Critics in Congress and in the news media often accuse agency regulators of having too cozy a relationship with the drug industry and favoring industry profits over patient safety. This chorus has grown in the past few years, as the agency has come under increasing scrutiny for a host of perceived blunders in approving new medicines and for being too slow to withdraw dangerous ones from the market. FDA regulates products representing approximately one-quarter of the American economy, so even small mistakes can have huge consequences.

The problem, which many critics fail to understand, is that *no drug is absolutely safe*. Even the most important life-saving medicines will often have potentially dangerous side effects that are not discovered until after the drugs have been approved. And many drugs later found to be dangerous provide tremendous health benefits to the vast majority of patients who use them. So, when deciding whether any given drug should be approved in the first place, or pulled from the market once potentially harmful side effects begin to emerge, the FDA must carefully balance its benefits against its risks.

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* *Jerome Arnett, Jr. is a physician practicing in Helvetia, West Virginia, and an adjunct scholar with the Competitive Enterprise Institute. Gregory Conko is a senior fellow at CEI.*

Still, as early evidence of negative side effects begins to arise, politicians and the news media demand that the FDA "err on the side of caution." The agency is often called upon to issue warnings or withdraw a drug based solely on preliminary and highly suspect information. When faced with this mounting political pressure, there is a real danger that the FDA will overreact—either by warning doctors and patients away from beneficial treatments or by withdrawing a drug from the market too quickly.

In 2004, for example, Democratic Rep. Bart Stupak (Mich.) and Republican Sen. Charles Grassley (Ia.) teamed up to accuse the FDA of intentionally dragging its feet in analyzing reports that a class of antidepressants was causing a sudden increase in suicides among teenagers using the drugs.[1] Sen. Grassley claimed that there was a coordinated effort within the agency to suppress the truth about these Selective Serotonin Reuptake Inhibitors (SSRIs), such as Prozac, Zoloft, and Paxil.[2]

Suicide is the third leading cause of death in teenagers after accidents and cancer, and the most important risk factor for suicide is depression[3]—so it would be doubly problematic if the very medical treatment prescribed to reduce depression actually raised the risk of suicide among this sensitive group. Unfortunately, as is often the case when it comes to food and drug regulation, politics trumped science in the FDA's decision making.

Although early reports appeared to indicate that children and adolescents taking SSRIs were more likely to experience "suicidal ideation"—thoughts about suicide—there was no evidence that SSRI use actually led to more deaths.[4] Nevertheless, politicians insisted that something be done to bring this supposed problem under control. The result was a stark warning about the alleged risk to children, teenagers, and young adults, which drove down antidepressant use among that group. That, in turn, had tragic consequences.

Early Warnings. Attention was first drawn to a potential problem with SSRIs in 2002, when the British Medicines and Healthcare Products Regulatory Agency issued a warning that adolescents treated with paroxetine—sold under various trade names, including Prozac—experienced "hostility, insomnia, tremor, dizziness, somnolence," and "emotional lability"—uncontrollable laughter, crying, or smiling—more often than patients treated with placebo.[5] A subsequent evaluation by the independent nonprofit organization Medical Letter found "no convincing data showing that SSRIs, including paroxetine, are any less safe in children than adults," and concluded that they were more likely to prevent suicide than to cause it.[6]

However, the FDA, unwilling to take this potential risk too lightly, began its own investigation. Based only on preliminary information, the agency issued health advisories concerning antidepressant use and teen suicide in October 2003 and again in March 2004.[7] In October 2004, after a 15-to-8 vote by its Psychopharmacologic Drugs Advisory and Pediatrics Advisory Committees, the agency required pharmaceutical companies to add a large "black box" warning in clear, bold-face type to the labeling of all antidepressants used with pediatric patients—recognized by prescribing physicians as the strongest warning the FDA can issue for a medication while still allowing its use. By

June 2005, prescriptions filled for children and adolescents had fallen by nearly 20 percent.[8] Yet it would soon become apparent that FDA's over-caution was resulting in greater harm than good.

Following imposition of the black box warning, the youth suicide rate—which had been steadily falling since 1987—rose by 14 percent from 2003 to 2004, the only increase of that magnitude during the 28 years in which such data has been collected.[9] And, while some dismissed the problem as a one-year anomaly, the increase was sustained into 2005. Over 600 more child and adolescent suicides than would otherwise be expected occurred during this two-year period, all as antidepressant use among this age group fell substantially.[10] By contrast, for adults over 60 years of age, the number of SSRI prescriptions continued to rise during this same period, while suicides in that age group declined.

The potentially harmful effects of the black box warning were not wholly unpredicted. Dr. Wayne Goodman, chairman of the department of psychiatry at the University of Florida and chair of the panel that advised FDA to order the black box warning, admitted that such a warning would make prescribing more difficult, and that it might alarm parents—but he insisted it was "worth that complication because it will raise the threshold for prescribing and force engagement in a discussion not only about the risks but the potential benefits of *alternatives to medications*."[11] Nevertheless, other panel members objected to the warning, and they pointed out that an estimated 2-percent increase in "suicidality"—a vague clinical concept that includes everything from passive death wishes to near-lethal suicide attempts—seemed small compared to the likelihood of a 15-percent increase in actual suicides if patients were left untreated.[12]

FDA's Bad Science. On what basis did the FDA make its final decision to impose the black box warning? Randomized controlled trials that pit the target product against another drug or placebo to test the particular hypothesis (in this case, suicidality) are considered to be the gold standard, but no such studies were available for SSRIs. Instead, the FDA based its black box warning on a meta-analysis of pooled data from 24 small studies with a total of 4,487 children and adolescents. Although they are a valuable tool, such studies are not wholly reliable due to differences in methodology and the patient populations included from study to study.

The FDA's meta-analysis found a weak association between SSRI use and suicidality—an increase from 2.1 percent for patients on a placebo to 3.8 percent for patients on SSRIs, a less than two-fold increased risk.[13] No completed suicides occurred among the patients in any of the studies, however.

The analysis had plenty of other weaknesses, as well. None of the data involved patients at the highest risk for suicide, because most of the 24 trials were conducted on patients who had been carefully screened to eliminate those at risk. Also, the trials included in the meta-analysis were too small and of too short a duration—around 12 weeks—to determine conclusively whether the risk of death from suicide increased or decreased. Studies substantial enough to show this require observational analyses of data from large

populations—but when studies become that large they lose the ability to account for biases and confounding factors, so any weak associations that are found are just as likely a result of random chance as they are from the studied drugs.

Furthermore, the FDA analysis found a less than two percentage point increase in suicidality—from 2.1 to 3.8 percent. Where the data are cloudy, as in this case, most statisticians agree that a threefold or greater increased risk is required to even suggest causation.[14] Perhaps most importantly, much other relevant information was ignored or minimized by the committees, including the fact that, overall, SSRIs have been found to *prevent* suicides in children and adolescents by treating the depression that gives rise to the risk of suicidality.[15]

In 2007, a re-analysis of the FDA's original studies, plus an analysis of seven additional studies, found a less than one percentage point rise in the correlation between SSRIs and suicidality, a result that was not statistically significant. The authors of that study concluded that the overall benefit-to-risk ratio was positive, meaning that the benefits of SSRI use outweighed the risks.[16] Other studies have reached similar conclusions.[17]

Conclusion. The FDA's overregulation of SSRI use has been a tragic failure. As Dr. Carolyn Robinowitz, then president-elect of the American Psychiatric Association, observed in 2007: "[B]lack-box panic is real…it is untreated depression that puts people at the greatest risk for suicide…antidepressants save lives."[18] And Kelly Posner, a Columbia University researcher who helped the FDA collect data on antidepressant use and suicide, told *The Wall Street Journal*: "If you look at the whole evidence puzzle, it points in one direction—antidepressants save lives."[19]

Unfortunately, this is only one in a long series of bad FDA decisions over many years that have kept good treatments off the market. For example, the agency's seven-year delay in approving beta blockers in 1981 for the prevention of second heart attacks cost an estimated 45,000 to 70,000 lives.[20] And its 1988 ban on advertising aspirin to the general public to prevent a first heart attack likely caused tens of thousands of deaths each year that the ban was in effect.[21] Centralized government overregulation takes away decisions that patients and their physicians are best suited to make for themselves. As economist Dr. Robert Higgs notes, forcing people at gunpoint to do "what's best for them" is the most reprehensible form of paternalism.[22]

In the end, this whole sordid story should serve as a warning to politicians, the news media, and especially to the incoming FDA Commissioner. It is essential that drug regulators not overreact to early evidence that a medicine may pose some heightened risk. After all, new medicines are approved only after they have been shown to benefit patients. Withdrawing drugs from the market too soon can have tragic results.

Notes

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[4] Anon., "Are SSRIs safe for children?" *Medical Letter on Drugs and Therapeutics*, vol. 45 (2003), pp. 53-54.
[5] SSRIs CSM working group report, http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con019472.pdf.
[6] Anon., "Are SSRIs safe for children?"
[7] J. Rosak, "New data show declines in antidepressant prescribing," *Psychiatric News*, vol. 40 (September 2, 2005), p. 1.
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[13] D.A. Brent, "Antidepressants and pediatric depression," *New England Journal of Medicine*, vol. 351 (2004), pp. 1598-1601.
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[18] Elizabeth Mechcatie, "FDA Scrutinizes Antidepressants, Risk of Suicidality: Warning may be applied to young adults," *Internal Medicine News*, vol. 40 (January 1, 2007), pp. 1-2; Elizabeth Mechcatie, "FDA Calls for Stronger Antidepressant Warning: Labeling should cite data on suicidality, and state that untreated depression is linked to suicide risk," *Internal Medicine News*, vol. 40 (May 15, 2007), p. 5.
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[20] D.H. Gieringer, "The Safety and Efficacy of New Drug Approval," *Cato Journal*, vol. 5 (Spring/Summer 1988), p. 190.
[21] P.H. Ruben, "FDA Advertising Restrictions: Ignorance is Death." In R. Higgs, ed., *Hazardous To Our Health? FDA Regulation of Health Care Products* (Oakland, Calif.: The Independent Institute, 1995), p 30.
[22] Robert Higgs, "Diminishing the Harm" in Higgs, ed. *Hazardous To Our Health?* p 100.