The Under Reported Story: ADHD, Stimulants, and the FDA

by Grace E. Jackson, MD
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Recently, the media minimized a crucial story which deserved to be front page news. Buried among the reports about Danish cartoons, Iraqi bombings, and domestic wiretaps was a recommendation from Food and Drug Administration safety advisors that stimulants, used in the treatment of 3 to 8 million children with ADHD, carry new warnings about the risks of heart disease, stroke, and death.

On February 9th 2006, members of the Drug Safety and Risk Management Advisory Committee *stunned* FDA officials with an 8 to 7 vote which called for the placement of Black Box Warnings on the labels of stimulants. For many industry watchdogs, the recommendation was long overdue.

It was only eight months ago that the FDA convened a similar hearing, partly in response to Health Canada's decision to remove Adderall XR from the market in early 2005. Although foreign authorities later rescinded that decision, concerns about the cardiovascular risks of Adderall *and other stimulants* remained. Dramatic media announcements preceded last June's deliberations, but the FDA leadership assured the public that no new warnings were warranted.

In their latest interviews with the press, FDA panelists cited a figure of 25 deaths (1999-2003) among American stimulant users, but 51 deaths are listed in an agency staff report. According to California neurologist, Dr. Fred Baughman, his Freedom of Information Act request revealed 186 deaths in the MedWatch database between 1990 and 2000. Given the fact that a mere 1% of all adverse events are believed to be filed with the FDA under the nation's voluntary reporting system, the true scope of stimulant lethality is much larger than the regulatory agency concedes.

Unfortunately for consumers, the cardiovascular risks of stimulants are hardly new. As early as 1977, Drs. Vernon Fischer and Hendrick Barner documented the cell changes associated with heart muscle enlargement in a chronic consumer of Ritalin (methylphenidate). Those findings were based upon a tissue biopsy obtained from the patient during bypass surgery. Intrigued by this discovery, Fischer teamed up Theodore Henderson in 1995 to publish the results of several animal experiments involving Ritalin. Their research confirmed a *causal* link between *normal* doses of the stimulant and the appearance of persistent heart cell abnormalities, identical to the changes observed in humans.

The connection between stimulants, cardiovascular disability, and death has long been documented in the medical literature, but physicians and government regulators have refused to acknowledge the hazards associated with prescriptions. In 2000, the FDA asked manufacturers to voluntarily remove the stimulant ingredient, phenylpropanolamine, from cold remedies and over-the-counter products used for weight control. In 2004, the FDA issued a rule to prohibit the sale of dietary supplements containing the stimulant, ephedra (ma huang). On January 13th 2006, the FDA issued a warning about the importation of Brazilian diet pills which contain a stimulant called Fenproporex. Each of these regulatory decisions stands in striking contrast to the agency's ambivalence about stronger warnings on the labels of ADHD drugs.

Many facts about stimulant medications, and the ADHD industry which sustains them, are commonly misreported or undisclosed. One example is the secret identity of atomoxetine (Strattera), a selective norepinephrine reuptake inhibitor approved by the FDA for children and adults in 2002. Widely marketed in the United States as the first "non-stimulant" for ADHD, the fact is that the World Health Organization designates the compound as a centrally acting sympathomimetic (psychostimulant), according to the international drug classification system. As neurologists at Stanford University have noticed, atomoxetine (and in Europe, the chemically similar reboxetine) possesses stimulant properties which make it an effective treatment for the sleep condition of narcolepsy.

While this classification dispute may seem trivial on the surface, it becomes salient in light of a recent report by North Carolina examiners who detected cardiac abnormalities in the autopsies of Strattera patients. If the FDA ever *does* decide to add Black Box Warnings about the vascular risks of *stimulants*, without acknowledging the true physiological effects of Strattera, one can expect Lilly's product to emerge as the clear winner of this year's safety lottery.

A word about regulatory authority is also in order. Contrary to the usual media reports, a Black Box Warning – which refers to the appearance of an explicit safety alert on the product label of a medication or medical device – is *not* the strongest precautionary measure in the Food and Drug Administration arsenal. The agency may require wording which outlines *contraindications*. These are statements about specific conditions or populations for which a medical product or device *must not be used*. Beyond the identification of contraindications, however, the FDA may issue advisories, enact rules, or implement enforcement decisions. Ultimately, the agency may initiate actions to remove a product from the market.

Reflective observers are wondering at this point *why stimulants have not been removed from the market* as a treatment for ADHD. Their concerns include the preliminary findings of Texan investigators, whose 2005 report in the journal *Cancer Letters* documented the emergence of chromosomal abnormalities in 12 out of 12 juveniles following three months of treatment with Ritalin. The unreported story is what happened *after* the behind-the-scenes scramble by officials from the FDA and other governmental bodies, who were dispatched to Houston last May in an effort to establish the validity of the methods and data of the Texan team. Subsequently authenticated, the implications of that research (namely, that Ritalin exposure in childhood may induce changes associated with higher risks of cancer) have been serious enough to trigger follow-up studies at other facilities.

FDA leaders continue to affirm that new warnings on stimulants are unnecessary. As Dr. Thomas Laughren and others have recently opined, ADHD is a serious medical condition for which the benefits of stimulant drug therapy outweigh the conceivable risks. Whether by ignorance or design, however, the regulators remain oblivious to the evidence-based limitations of the prescription pad: at least 40% of all children fail to tolerate or respond to stimulant therapy; about twice as many respond at least as well to non-pharmacological interventions; and, as documented in the National Institute of Mental Health's most prestigious study to date (the MTA study), the long term outcomes for medicated children demonstrate diminishing returns over time, persistent suppression of growth (about 1 cm per year), and artificial behavioral improvements which dissipate when treatment is withdrawn.

The FDA and others are disingenuous when they ignore the contentious nature of identifying ADHD as a neurological disorder for which medications are the best solution. A strong body of evidence now challenges both assertions. Clinicians question the ethic of drugging children *and* adults, in an effort to suppress symptoms which may be interpreted as transient, developmental delays (most children outgrow ADHD in their teens); normal variants of temperament; contextually appropriate reactions; and/or the failure of caregivers, social systems, or culture to assist others in maximizing their capacities for moral agency and self-control.

It is time for consumers, physicians, educators, and policy makers to confront the distorted and missing information which surrounds the phenomenon of ADHD. More members of the medical community should doubt the legitimacy of the condition, since no biological marker or diagnostic test has been found or devised. When interviewed, a majority of physicians state that they would prefer *not* to prescribe stimulants to children, due to the physical and psychological side effects. Not surprisingly, the world community observes the United States with alarm for the unjustified chemical exploitation of those who are different, but not diseased.

References

Alonso-Zaldivar, R. (2006, February 10). Warning Urged for ADHD Drugs: An FDA panel cites heart risks in its advisory on Ritalin and similar medications. Retrieved February 14, 2006, from http://www.latimes.com/features/health/medicine/la-na-fda10feb10,1,7089625.story?coll=la-health-medicine.

Doggett, A.M. (2004). ADHD and drug therapy: is it still a valid treatment ? *Journal of Child Health Care, 8,* 69-81.

Dooren, J.C. (2005, July 1). FDA panel wants clearer ADHD labels: Agency asked to proceed with plans for warnings about hallucinations and suicide risk. CNN Money. Retrieved July 27, 2005, from http://money.cnn.com/2005/07/01/news/fortune500/fda_panel.dj

El-Zein, R.A., Abdel-Rahman, S.Z., Hay, M.J., Lopez, M.S., Bondy, M.L., Morris, D.L., and Legator, M.S. (2006). Reply to Letter to the Editor. *Cancer Letters*, *231*, 146-148.

_____. (2005). Cytogenetic effects in children treated with methylphenidate. *Cancer Letters*, *230*, 284-291.

Faraone, S.V., Biederman, J., and Mick, E. (2005). The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychological Medicine, 35,* 1-7.

Fischer, V.W. and Barner, H. (1977). Cardiomyopathic findings associated with methylphenidate. *JAMA*, *238*, 1497.

Fischer, V.W., and Henderson, T.A. (1994). Effects of Methylphenidate (Ritalin) On Mammalian Myocardial Ultrastructure. *The American Journal of Cardiovascular Pathology, 5,* 68-78.

Garside, D., Ropero-Miller, J.D., Riemer, E.C. (2006). Postmortem tissue distribution of atomoxetine following fatal and nonfatal doses – three case reports [Abstract]. *Journal of Forensic Sciences, 51,* 179-182.

Harding, K.L., Judah, R.D., and Gant, C. (2003). Outcome-based comparison of Ritalin versus food-supplement treated children with AD/HD. *Alternative Medicine Review, 8,* 319-330.

Hill, J.C. and Schoener, E.P. (1996). Age-dependent decline of attention deficit hyperactivity disorder. *American Journal of Psychiatry, 153,* 1143-1146.

Jackson, G.E. (2005). *Rethinking Psychiatric Drugs: A Guide for Informed Consent.* Bloomington, IN: Author House.

Larossa, O., de la Llave, Y., Bario, S., Granzio, J.J., and Garcia-Borreguero, D. (2001). Stimulant and anticatalepic effects of reboxetine in patients with narcolepsy: a pilot study [Abstract]. *Sleep*, *24*, 282-285.

Poulton, A. (2005). Growth on stimulant medication; clarifying the confusion: a review. *Archives of Disease in Childhood*, *90*, 801-806.

Rafalovich, A. (2005). Exploring clinician uncertainty in the diagnosis and treatment of attention deficit hyperactivity disorder. *Sociology of Health & Illness*, *27*, 305-323.

Reuters News Service. (2006). FDA Reports 51 deaths of attention drug patients. Retrieved February 14, 2006, from: http://abcnews.go.com/US/print?id=1595545.

Rossiter, T. (2004). The Effectiveness of Neurofeedback and Stimulant Drugs in Treating AD/HD: Part II. Replication. *Applied Psychophysiology and Biofeedback*, *29*, 233-243.

Singh, I. (2005). Will the "Real Boy" Please Behave: Dosing Dilemmas for Parents of Boys with ADHD. *American Journal of Bioethics*, *5*, 34-47.

U.N. Committee on the Rights of the Child. (2005, September 30). Consideration of Reports Submitted by States Parties Under Article 44 of the Convention. Retrieved October 06, 2005, from http://www.ohchr.org/english/bodies/crc/docs/co/CRC.C.OPSA.CO.2new.pdf

Wallis, C. (2006, February 10). Getting Hyper About Ritalin: Why an FDA advisory panel suggested strong warnings for Ritalin, freaking out parents and patients – and even doctors [Electronic Version]. *Time*. Retrieved February 14, 2006, from http://www.time.com/time/health/printout/0,8816,1158901,00.html.