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Ethical Human Psychology and Psychiatry, Volume 7, Number 2, Summer 2005

EDITORIAL

Methylphenidate-Induced Neuropathology in the Developing Rat Brain: Implications for Humans

Imagine the following experiment. Researchers administer a certain drug to young rats, and subsequently find that the drug has harmful long-term effects. This straightforward experiment has been done numerous times with numerous drugs. It is common for the researchers, in their published papers, to at least make some suggestions about what the findings in rats might mean for human brain development. If the drug in question is illicit, the results are usually held up as one more reason to refrain from using the drug. If the drug happens to be a prescription drug, most scientists would at least *suggest* the need for increased caution by the medical profession—especially if the drug's target market is young children.

Interestingly, the above experiment was recently conducted with a common drug given to millions of children. The study was done by William Carlezon and his colleagues at Harvard Medical School (Carlezon, Mague, & Anderson, 2003). The drug in question? Ritalin. And, indeed, the researchers discovered that Ritalin has harmful long-term effects on the developing rat brain. In their study, young rats exposed to Ritalin had an increased risk for depression later in adulthood.[1] You would think that this would at least *suggest* that children diagnosed with attention deficit hyperactivity disorder (ADHD) and given Ritalin *might* be at risk; however, this straightforward conclusion poses a significant public relations problem for the people responsible for the rapid increase in the use of Ritalin in this country. But, given their astute public relations skills and the inability of the press to critically analyze scientific reports, the obvious conclusion had little chance of making the news. Instead, a flawed series of illogical steps in thinking resulted in the media reporting that the main message of the study is that children need an accurate diagnosis of ADHD. How did this happen?

Let's start with the American College of Neuropsychopharmacology's (ACNP) press release about the study (Lobliner, 2004). Amazingly, the press release concluded that the study only has implications for "normal" children and not for children diagnosed with ADHD. In fact, not only does the ACNP forgo the slightest suggestion that Ritalin *might* be harmful for "ADHD" children, it goes out of its way to explain that the results do not apply to "ADHD" children. According to their logic, only if you have an *incorrect* diagnosis of "ADHD" will Ritalin be harmful. It is interesting to examine how a press release takes data, showing that Ritalin harms the brains of rats, and then turns that data into the message that Ritalin will only harm children with an incorrect diagnosis.[2]

The major flaw in their logic starts with the explanation that the rats in the study were not "ADHD" rats but "normal" rats. Labeling the *rats* as normal allows the ACNP to assert that the findings only have implications for normal *children*. The ACNP has basically

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established a dual role for Ritalin. On one hand, Ritalin is beneficial for children diagnosed with ADHD; yet, on the other hand, it is harmful to "normal" children. Their reasoning would be more acceptable if there were any anatomical, genetic, or biochemical markers to differentiate between "ADHD" and "normal" in humans—or rats. When one considers that even drawing a line between "ADHD" and "normal" varies widely from one doctor's office to another, from one state to another, or from one country to another, the idea that there is some scientific reasoning involved in where to draw this line is hard to accept. If a committee ever developed a universal standard for ADHD, would Ritalin's apparent dual action—beneficial to some, but harmful to others—fall in line with the committee's decision? (The fact that no committee has ever come up with any workable standard to diagnose ADHD speaks volumes about the science to begin with.)

If Ritalin only produces harmful effects on the "normal" brain, then whose definition of "normal" do we accept? Many children in other parts of the world would not be given a diagnosis of ADHD in their own countries, but in America they are easily labeled with ADHD. A correct diagnosis in America might not be the same as a correct diagnosis in their home country. Would Ritalin's effect on the brain follow their home countries' definition of ADHD or America's definition?

The ACNP's reasoning would also be more acceptable if the beneficial effect of Ritalin—a short-term increase in attention span—was dependent on a diagnosis of ADHD. But the beneficial effect of Ritalin holds true for everyone, whether diagnosed with ADHD or not. Ritalin will improve everyone's attention span—even people *misdiagnosed* with ADHD.

As an example of the problem with the ACNP's logic, imagine these two scenarios. The parents of a young teenage boy are concerned about his grades and take the boy to a psychiatrist (Cohen & Leo, 2002). After completing a short questionnaire the boy is diagnosed with ADHD and given a prescription for Ritalin. According to the ACNP, the Ritalin for this boy will have a beneficial effect. Another boy, who is a classmate of the first boy, has a week of exams coming up and wants to improve his grades, so he decides to buy some Ritalin from the first boy. According to the ACNP, Ritalin will harm this boy. The idea that Ritalin is *not* harmful to the boy whose parents filled out a short checklist but is harmful to the boy who bypassed the checklist is problematic.

The ACNP's press release quotes the lead researcher's conclusions that "Ritalin can be highly effective in the treatment of ADHD, but our work highlights the importance of getting a proper diagnosis." However, a more accurate conclusion would have been: "Our study, which documents that Ritalin is harmful to the developing *rat* brain, suggests that Ritalin might have similar effects on the developing *human* brain" (Period. End of story.).

This recent study is very similar to the ADHD neuroimaging research that, based on comparisons of "ADHD" children to "normal" children, has supposedly documented an organic pathology associated with the diagnosis of ADHD. The problem, which the imaging researchers have mostly ignored, is that the overwhelming majority of the ADHD children in their studies have a prior history of stimulant medication (Baughman, 1998; Leo & Cohen, 2003). Thus, the ADHD imaging research at least suggests that Ritalin might be harmful to the developing brain. However, in the current environment, any data suggesting that Ritalin might harm the developing brain must be "explained."

Unfortunately, the damage control works. With little change from the original ACNP press release, 1 month later *The Wall Street Journal* uncritically reported the ACNP's version of the study, "This latest research has particular significance for healthy children who have been wrongly diagnosed and put on ADHD medication" (Parker-Pope, 2005). But *The Wall Street Journal* has completely missed the big picture. There is no good reason to

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limit the significance of this study to *misdiagnosed* children. Indeed, this research has particular significance for *all children* taking Ritalin, whether it was prescribed by a doctor or not. In the rat world there is no line between "normal" and "ADHD," and there is no reason for the ACNP or *The Wall Street Journal* to draw one. *The Wall Street Journal*'s uncritical acceptance of the ACNP's spin on this research is just one more reason to be skeptical of the media's ability to accurately portray science.

In addition, the ACNP provides no guidelines on how psychiatrists can identify children with an "incorrect" diagnosis. For many people, the diagnosis sounds scientific and complicated, but it is neither. Imagine a random sample of difficult to handle, ten-year-old boys who are prescribed Ritalin for ADHD. If the parents, teachers, and psychiatrists all agree that Ritalin makes the boys easier to control then essentially the boys have received a correct diagnosis, at least according to current psychiatric practice. Other than adult satisfaction with the drug's performance there are no other factors to determine if the diagnosis is correct. On what grounds could the ACNP possibly tell some of these parents that their children have an "incorrect" diagnosis?

However, putting all of these arguments aside, does anyone believe that the ACNP's press release and subsequent media coverage would have gone into complicated discussions about the difference between "normal" and "ADHD" if the scenario had been reversed; and, instead of harmful effects, beneficial effects from Ritalin had been found in these rats? With beneficial effects, there would have been no need to draw a line between "ADHDs" and "normals." Interestingly, for an example of this angle, one needs to look no further than *The Wall Street Journal* article. Indeed, the author notes that the study did find a beneficial effect of Ritalin: that early exposure to Ritalin results in less interest in cocaine later in life. When it comes to discussing the beneficial effect, there is suddenly no reason at all to draw a line between "normals" and "ADHDs." According to *The Wall Street Journal*, this finding "suggests that kids exposed to Ritalin probably aren't at higher risk for abusing drugs." Since there are no biological markers, apparently, whether a rat is a "normal" rat, or an "ADHD" rat, or just a plain old laboratory rat, all depends on the message you want to send about your drug.

NOTES

1. The study discussed in my essay and presented at the ACNP's annual conference has not been published. But, via e-mail, the primary author reported that the conference presentation was largely based on the paper I have cited.

2. The contact person for this press release, Jill Lobliner, reported that the press release was written by the ACNP. It is unclear who the actual author of the press release is.

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