

Stimulant Use in ADHD, Bipolar Discouraged

Expert in mood disorders cites evidence showing that amphetamines might worsen both illnesses.

BY PATRICE WENDLING

CHICAGO — Dr. Nassir Ghaemi is a bit of a maverick. The well-published author and director of the mood disorders and psychopharmacology programs at Tufts Medical Center in Boston likes to step off the well-worn CME lecture track and challenge his audience with the words of ancient philosophers, artists, and economists.

At the annual meeting of the American Academy of Clinical Psychiatrists, he pushed those in attendance even further, asking them to reconsider the widely held view that stimulant treatment is relatively safe in attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder.

Dr. Ghaemi contends that children and adults who are diagnosed with ADHD in the United States are automatically given amphetamines, and that there is a routine presumption that long-term treatment with these agents is warranted. He said he believes amphetamines should only be used as a last resort and primarily for short-term treatment in ADHD. In bipolar disorder, he takes the stance that amphetamines should be used even more sparingly—if at all.

The cornerstone of Dr. Ghaemi's arguments lies in emerging evidence that amphetamines might actually worsen ADHD and bipolar disorder.

Some of the first glimmers of this came nearly a decade ago from two retrospective pediatric studies showing a correlation between stimulants and mania. In 42 children with bipolar disorder and ADHD, the mean age of onset of ADHD was 5.5 years, mean length of stimulant use 6.9 years, and onset of manic symptoms 7.1 years (*J. Am. Acad. Child Adolesc. Psychiatry* 2000;39:713-20).

In 34 adolescents hospitalized with mania, patients with stimulant use before the onset of bipolar disorder had an earlier age at onset of the disease than those without prior stimulant exposure (10.7 vs. 13.9 years). Additionally, adolescents treated with at least two stimulants had a younger age at onset than those treated with one stimulant (*Bipolar Disord.* 2001;3:53-7).

"It's all association, correlational, observational; it's not definitive, it's not causative, but there's room for suspicion that amphetamines might be causing mania in these children," said Dr. Ghaemi, also a professor of psychiatry at Tufts University who completed a research fellowship in psychopharmacology at Massachusetts General Hospital.

He went on to highlight additional data on treatment-emergent mania. In a brief open study in 14 depressed adults with a DSM-IV diagnosis of bipolar illness treated with methylphenidate added to a mood stabilizer regimen, 3 patients (21%) stopped methylphenidate because of anxiety, agitation, or hypomania (*Bipolar Disord.* 2000;2:56-9).

A case review of 82 children (mean age 10.6 years) with bipolar disorder not receiving mood stabilizers reported treatment-emergent mania in 20% of 40 children on stimulants—6 of 28 children on methylphenidate and 2 of 12 on amphetamines. The mean time to mania onset was 12.5 days from start of treatment (*J. Affect. Disord.* 2004;82:149-58).

By themselves, these data are not that alarming, given that antidepressants in the observational setting are associated with roughly a 20% mania switch rate, Dr. Ghaemi said. In the case review, however, long-term harmful effects were observed, including more mood episodes, suicidality, and hospitalization.

In his own study, co-led by former Emory University colleague Dr. Aliza Wingo, the rate of stimulant-associated mania or hypomania reached a staggering 40% in 137 adults with ADHD and bipolar disorder treated mostly with methyl phenidate for varying lengths of time (*Psychopharmacol. Bull.* 2008;41:37-47). "This is the largest study of adult ADHD bipolar comorbidity, and we're finding that stimulants are harmful in almost one-half of patients," he said.

Routine and long-term amphetamine use in young children is particularly concerning, Dr. Ghaemi said, because animal studies have shown an association between early amphetamine use and adult neurobiologic effects, including decreased response to rewarding stimuli, increases in depressive and anxiety behaviors, and decreased dopaminergic neuronal activity. In rats given Ritalin at a dose of 2.0 mg/kg twice daily from days 20 to 35 after birth, researchers observed a significant decrease in long-term survival of newborn cells, particularly in the temporal hippocampus (*Biol. Psychiatry* 2006;60:1121-30).

The way in which this plays out in bipolar disorder is even more remarkable, as the illness itself can reduce cortical thickness, Dr. Ghaemi said. Brain MRIs identified significant decreased cortical thickening in multiple prefrontal cortices in 25 patients with bipolar disorder, relative to 21 healthy controls (*Bipolar Disord.* 2006;8:65-74). In addition, a correlation was found between illness duration and cortical thinning.

"Amphetamines, if they were newly coming to the market today, I believe they wouldn't make it through [Food and

Drug Administration] screening because of this issue," he said. (The agency has looked recently at the use of stimulants in children and adolescents with ADHD. See article below.)

Dr. Ghaemi's thinking is not so radical, according to Dr. Boghos Yerevanian, clinical professor of psychiatry, University of California, Los Angeles, and director of the mood disorders program at Greater Los Angeles VA Healthcare/ Sepulveda.

"I agree with Dr. Ghaemi's observations; they are wise words," Dr. Yerevanian said in an interview. "There are some data, not as well studied as [they] should be, that long-term stimulant treatment is associated with brain microvascular disease. This further complicates the problem with bipolars whose brain integrity is already compromised due to various factors, some of it known and most unknown.

'It's all association, correlational, observational; ... it's not causative, but there's room for suspicion that amphetamines might be causing mania' in children with bipolar.

Stroke, of course, is associated with cocaine use in young people and cocaine in many respects mimics amphetamines."

The next step is for the biologic data to be taken into monkey and human studies, and for the current evidence to be more widely disseminated, Dr. Ghaemi said. "I'm not saying you should stop using amphetamines, but you should think about these data when you're using amphetamines."

Dr. Ghaemi reported that in the past year he has received research support from Pfizer Inc. and honoraria from Bristol-Myers Squibb. He was on the speakers bureau for Pfizer and Astra-Zeneca but is not currently. ■

To watch a video interview of Dr. Ghaemi, go to www.youtube.com/watch?v=aWuxgMtZxZY.

Data on ADHD Stimulants Deemed Not 'Threatening'

BY HEIDI SPLETE

Stimulant use was significantly associated with sudden, unexplained deaths in children and adolescents in a study of more than 500 children, but the data are not sufficient to change clinical prescribing practices, Food and Drug Administration officials said in a press briefing.

"It's hard to characterize the results as reassuring, but we didn't find them threatening," said Dr. Robert Temple, director of the Office of Drug Evaluation I at the agency's Center for Drug Evaluation and Research.

Previous studies suggest that stimulants increase the risk of cardiovascular events, including sudden death, in children who are already at risk for heart problems, Dr. Temple said. But few data exist on the impact of stimulant use in children without known underlying risk factors, he noted.

In this study, Madelyn S. Gould, Ph.D., of Columbia University in New York, and her colleagues compared stimulant use in 564 children aged 7-19 years who died suddenly from no known health problems, with stim-

ulant use in 564 children aged 7-19 years who died as passengers in motor vehicle accidents.

Accident victims were chosen because they provide a control population of children who died suddenly and whose death was not caused by a known health problem. Children with a known history of heart problems were excluded from the study (*Am. J. Psychiatry* 2009 June 15 [doi: 10.1176/appi.ajp.2009.09040472]).

The researchers found that 10 (1.8%) children who died suddenly of unexplained causes were taking stimulants, compared with 2 (0.4%) children who died suddenly in car accidents. This difference was statistically significant after controlling for multiple variables, but the study was limited by several key factors, including a lack of complete postmortem blood work on the car accident victims, the researchers wrote.

A case-control study cannot prove causality, Dr. Temple added. "The reason for our cautious interpretation is that everything depends on whether the people who died were or were not taking an amphetamine," he said, adding that the researchers depended primarily on the memories of people involved with the accident victims.

"We were unable to conclude that the data affect the overall risk and benefit profile of the stimulant medications," said Dr. Temple.

He advised clinicians who treat children with stimulants to adhere to the current labeling recommendations and to monitor the children closely. "We continue to advise people to look at these children for any evidence of an underlying cardiac disease."

Two additional studies on the effects of stimulant use and cardiovascular outcomes are in progress, one in children and one in adults, said Dr. Gerald Dal Pan, director of the Office of Surveillance and Epidemiology at the Center for Drug Evaluation and Research.

These studies will evaluate the impact of stimulant use on sudden cardiac death, heart attack, and stroke. Results of the child study are expected in the fall, and results of the adult study are expected early next year, he said.

To view the full study, go to www.ajp.psychiatryonline.org/cgi/reprint/appi.ajp.2009.09040472v.

The study was cofunded by the FDA and the National Institute of Mental Health. Dr. Gould had no financial conflicts to disclose. ■