

## Medical News &amp; Perspectives

## Chess Study Revives Debate Over Cognition-Enhancing Drugs

Jeff Lyon

A placebo-controlled study suggesting that cognition-enhancing drugs (CEs) can improve a chess player's performance and a related survey indicating that nearly 10% of ranked German chess players have taken them during competition have thrown the spotlight once again on "smart pills," their purported benefits, and uncharted dangers.

About a decade ago, reports filled the general and scientific media about the illicit use of such CEs as methylphenidate, a stimulant used to treat attention-deficit/hyperactivity disorder (ADHD), and modafinil, a wakefulness agent used to treat narcolepsy, sleep apnea, and shift work disorder, by students and others who were taking them to improve performance on examinations or in the workplace. There were stories about the risks and ethics of such behavior, countered by calls from some neuroscientists for a more open mind about the drugs and their positive side. The field of brain augmentation was even given a chic new name, *cosmetic neurology*.

While media attention has since waned, the underground use of CEs seemingly has not. A 2013 survey found that 19.9% of the 1105 German surgeons who responded admitted to having taken a prescription or illicit drug to enhance cognition at least once. Another study found that 61.8% of undergraduates at the University of Maryland had been offered prescription stimulants for nonmedical purposes, most of them by friends with prescriptions, and 31% had used them.

And the trend "hasn't peaked yet," noted Barbara Sahakian, DSc, a professor of clinical neuropsychology at the University of Cambridge who investigates the effectiveness of CEs in treating the cognitive impairment associated with certain psychiatric disorders.

Sahakian cited more subgroups flocking to bootleg CEs—academics facing publish-or-perish pressure, sleepy physicians rounding at night, business executives fighting jet lag in different time zones—and said such widespread nonmedical use by those without cognitive deficits worries her



because little is known about the drugs' safety and addictive potential over time.

"We have no long-term studies in healthy people showing that they are safe," she said, "or whether they are used to cope with one-off events or are part of a daily routine. We don't know much about use patterns."

Adding to the muddled picture is the apparently widespread clinical practice of prescribing CEs off-label, in particular modafinil, which is thought to be among the most well-tolerated of the drugs. According to some reports, the number of patients receiving modafinil prescriptions for off-label use increased by more than 15-fold from 2002 to 2009. In the same period, on-label prescribing of the drug increased by less than 3-fold.

Across all years, 89% of patients prescribed modafinil did not have an on-label diagnosis, wrote the authors.

### Nonmedical Brain Boosting

Covert use of CEs by healthy people to gain an edge has drawn the interest of Klaus Lieb, MD, director of the Department of Psy-

chiatry and Psychotherapy at the University of Mainz, and his German and Swedish research partners.

After conducting the survey of German surgeons indicating that 1 in 5 have used CEs to boost their brainpower, Lieb's team turned its attention to the efficacy of such drugs. Could they, for instance, make people better at chess?

A group of 39 highly rated male members of the German Chess Federation were enlisted to play more than 3000 15-minute games against computers matched to their skill levels while taking modafinil, methylphenidate, or caffeine. The researchers reported that players taking modafinil and methylphenidate won more games overall, though they pondered their moves longer, causing them to sometimes lose on time.

The positive association surprised Lieb. "Our hypothesis [had been] that it's not possible to enhance subjects who are already working at top performance," he said.

The result was disturbing on its own, since it implied that the venerable board game was vulnerable to doping. But then

## Clinical Picture for Cognitive Enhancers

Beyond their long-standing use in treating ADHD, cognitive enhancers (CEs) are also being tested in the clinical treatment of the following medical conditions:

### Neurodegenerative Disorders

Cognitive enhancers such as acetylcholinesterase inhibitors, which increase the availability of the neurotransmitter acetylcholine, have been tested in mitigating cognitive decline in Alzheimer disease, Parkinson disease, and dementia with Lewy bodies. Acetylcholinesterase inhibitors like donepezil and rivastigmine have shown a modest measure of [success](#).

### Major Depression

Cognitive enhancers like the serotonin modulator vortioxetine and the wakefulness drug modafinil have shown promise in alleviating the intellectual fog that can accompany major depression and sometimes persists even after the mood disorder itself lifts. One recent [study](#) suggested that modafinil improved episodic and working memory in remitted patients, and a [meta-analysis](#) of 3 studies concluded that vortioxetine "significantly" improved cognition in depressed patients.

### Schizophrenia

Although studies of schizophrenia have implicated dysfunction of the glutamate receptor *N*-methyl-D-aspartate, efforts to treat the disease with CEs that modulate glutamate have thus far been disappointing. However, some experts [note](#) that most of trials have involved older, mostly male patients who are least likely to benefit.

### Down Syndrome

Several [studies](#) have shown that compounds that target GABAergic neurotransmission can improve learning and memory in mouse models of the chromosomal disorder by rescuing underlying deficits in hippocampal synaptic plasticity. [Human trials](#) are currently under way to evaluate the efficacy of the  $\gamma$ -aminobutyric acid<sub>A</sub> receptor antagonist pentylentetrazole in improving the intellectual abilities of patients with Down syndrome aged 13 to 35 years.

### Autism

Cognition enhancing drug [interventions](#) similar to those being tested in Down syndrome have been proposed, as reduced GABAergic signaling seems to play a role in the pathophysiology of autism as well.

legitimizing the nonmedical use of CEs, particularly modafinil.

Modafinil, a US Food and Drug Administration (FDA)-approved eugeroic, increases cortical catecholamine levels while indirectly upregulating cerebral serotonin, glutamate, orexin, and histamine and downregulating  $\gamma$ -aminobutyric acid (GABA) levels. Its status as a [front-runner among CEs](#) is based on studies that have evaluated its effects on people with cognitive difficulties related to mental disorders, as well as other studies performed on medically fit volunteers.

Sahakian, herself, conducted such a [trial](#) on healthy subjects in 2013, finding that the drug significantly improved performance on tests of executive function, including working memory and cognitive flexibility. Furthermore, it raised the subjects' engagement level. As she told *JAMA*, "Modafinil not only improved test performance but task-related motivation as well. It didn't make them euphoric. It just made them enjoy the task better."

Pivotal was a 2015 [meta-analysis](#) of 24 studies published from 1990 to 2014 that examined modafinil's impact on healthy, nonsleep-deprived humans. The review concluded that the drug sharpened decision making and planning and likely improved attention and learning as well.

the researchers discovered something more. Employing an online survey and a randomized mailed questionnaire, they polled members of the German Chess Federation as to their past use of psychoactive substances, including not only modafinil and methylphenidate, but amphetamines,  $\beta$ -blockers, ephedrine, and cannabis. Using a randomized response technique to guarantee anonymity, they reported that 8.9% of respondents admitted to having used prescription or illicit drugs at one time or another to improve their chess play.

The finding troubled some physicians, among them Anjan Chatterjee, MD, of the Center for Cognitive Neuroscience at the University of Pennsylvania, who has written extensively on the pluses and minuses of making CEs more available for nonmedical use.

Chatterjee found the cheating revelation disquieting, calling it "a symptom of modern society, where progress and productivity are valued over everything else."

He said the national conversation about the ethics of CEs had subsided

recently because of an overall downturn in the drug industry's investment in neuropharmaceuticals. "There's so much excitement about biologics and cancer that a lot of pharma's oxygen is getting sucked into that area. Plus the brain is really hard. There hasn't been much change in the efficacy [of CEs] in 50 years."

### Questioning Cognitive Enhancement

Chatterjee describes himself as "on the fence" about the nonmedical use of CEs by people without cognitive deficits. But some commentators like Henry Greely, JD, of Stanford University's Program in Neuroscience and Society, are unabashed supporters. Greely collaborated on a 2008 [essay](#) titled "Towards Responsible Use of Cognitive Enhancing Drugs by the Healthy" that appeared in *Nature*.

"I have the bias that more cognitive capacity could lead to better societies," he said.

One of Greely's collaborators on the 2008 *Nature* article was Sahakian, who counts herself as a conditional advocate of

### Safety Concerns

To Sahakian, though, the central question is less about efficacy than safety, particularly since population-based safety data on any of the CEs in healthy people are scarce. What is known about the drugs' action over time is based on their use in the clinic (see [Box](#)), where physicians are licensed to prescribe drugs only to correct medical conditions—not to help healthy CEOs deliver presentations to investors. In the former context, adverse effects of CEs must be balanced against therapeutic benefits.

For patients with ADHD, for example, the indicated drugs are methylphenidate, atomoxetine, and a combination of amphetamine and dextroamphetamine. In this clinical population, their side effects and adverse events, observed over many years, range from nausea and dry mouth to heart attack and stroke. But their use in all but those patients with serious [heart problems](#) is deemed worth the risk.

As Sahakian pointed out, however, the cost-benefit equation is murky for the use of

CEs in healthy young people who are among the biggest underground users.

"We now know that the frontal lobes are one of the last parts of the brain to complete development, so one has to learn if those under 25 who do not have ADHD should be taking them," she noted.

The potential for developing substance use disorder symptoms is of particular concern for healthy individuals using [amphetamines](#) or [modafinil](#).

Prior to her 2013 study, Sahakian sought permission to follow her healthy volunteers over an extended period to see if any adverse outcomes appeared. "But the ethics committee wouldn't pass it," she said.

Longitudinal studies are indeed needed, said Lon Schneider, MD, MS, a professor of psychiatry, neurology, and gerontology at the University of Southern California who advises on clinical trial methodology

and drug development. Previous trials of CEs in the healthy have been small, of spotty quality, and so varied in approach and metrics that comparisons are difficult, he noted. But large, systematic trials of efficacy and safety in otherwise healthy individuals, of the kind designed to elicit approval by the FDA, are not feasible at this time.

"In the current regulatory climate [the] FDA will not license drugs for use in non-medical conditions or to improve performance [among the unimpaired]," he said.

Some think a case might at least be made for legitimizing the use of CEs in otherwise healthy seniors who fear losing their former mental acuity.

"Let's say you are in your 60s and 70s," said Sahakian. "You don't have dementia, but you're losing some sharpness. You just want to get some of your old faculties back. Is that enhancement? Or is it restoration?"

Sharon Straus, MD, MSc, a gerontologist at the University of Toronto, is wary of prescribing CEs for mild cognitive impairment in the elderly because of adverse effects, including diarrhea, vomiting, fatigue, insomnia, and weight loss that have been noted among patients with Alzheimer disease.

"There is no high-quality evidence to support use of cognitive enhancers in healthy people," said Straus, who is director of the Knowledge Translation Program at St Michael's Hospital in Toronto. "I would advise clinicians to avoid their use."

She notes that there are alternative interventions known to stave off cognitive decline, including exercise, tobacco cessation, and weight loss, though she acknowledges that they are difficult to implement.

"I think people are looking for a magic bullet." ■

**Note:** The print version excludes source references. Please go online to [jama.com](http://jama.com).