



Organizers of the ESL One Cologne competition tested video gamers for smart drugs for the first time last year — all the tests came back clean.

SMART DRUGS

A dose of intelligence

As mind sports becomes the new frontier for doping concerns, research is exploring whether users really get any value from ‘smart drugs’.

BY AMBER DANCE

In August 2015, 80 professional video gamers from around the world gathered for the ESL One Cologne competition in Germany. With US\$250,000 in prize money up for grabs, pressure was high, and competition organizer ESL wanted to ensure fair play. At some point during the two-day event, a random selection of players received a tap on the shoulder and were escorted to a discreet back room where a physician awaited.

For the first time in its 16-year history, ESL was taking saliva samples on its lookout for dope. Smart drugs were allegedly circulating, helping players to get in the zone. “Just like in normal sports, it’s not OK to win because you took a pill,” says Anna Rozwandowicz, ESL’s director of communications and the first head of its anti-doping initiative. That weekend, all the tests came back clean.

E-athletes aren’t the only ones allegedly popping pills to try to enhance their mental faculties. Use of the drugs seems to be common, although finding firm data is not easy. In 2014, a survey of British and Irish students reported that more than 3% currently used prescription medications as cognitive enhancers¹. A 2013 survey of surgeons found that nearly 20% had used medication for cognitive enhancement

at least once². And an informal survey (go.nature.com/xmlrn2) from 2008 reported that a similar proportion of *Nature* readers had used medications off-label to improve memory or concentration.

Many smart drugs are prescription medications either purchased illegally or used off-label. Top choices include Adderall (amphetamine) and Ritalin (methylphenidate) — treatments for attention-deficit hyperactivity disorder (ADHD) — and modafinil, which is a medication for sleep disorders such as narcolepsy. In people with ADHD or sleep disorders, these drugs can raise brain function so that it matches that of healthy people. But it is not clear whether the same medications can push a neurologically healthy, well-rested individual onto a higher cognitive plane. There is also the question of side effects. Despite these uncertainties, the apparently widespread use of neuroenhancers has prompted an ethical debate about whether their use is fair in school exams or mental games.

LIKE A BOSS

It is hard to say just how much these medications help an average person. Amphetamines improve focus and can make dull tasks seem interesting. So they might change a student’s perspective from, ‘Ugh, chemistry’, to ‘Ooh!

Carbon bonds!’ — even though that student is not any brighter. “They don’t really live up to the name smart pills,” says Martha Farah, a cognitive neuroscientist at the University of Pennsylvania in Philadelphia. “Nothing that would turn you from a B to an A student or suddenly give you winning business ideas.”

It’s still not clear precisely how these drugs produce their effects. Adderall and Ritalin are the best understood. Their main effects seem to relate to the neurotransmitters noradrenaline and dopamine, each of which mediates several effects, including attention and reward. Normally, a neuron releases these neurotransmitters as a message, telling other neurons to fire or stay quiet. Once the signal has been received, the first neuron re-absorbs the neurotransmitters. These medications block that re-uptake, so that the signals persist. Amphetamines also have other actions, such as preventing the breakdown of neurotransmitters.

Understanding of the cognitive-enhancement mechanism of modafinil is more sketchy. The drug affects “pretty much every major neurotransmitter in the brain”, says Ruairidh Battleday, a neuroscientist at the University of California, Berkeley. These include dopamine and noradrenaline, so part of its effect is probably similar to that of Adderall and Ritalin.

STEPHANIE WUNDER/ESL

Extra neurotransmitters help parts of the brain to communicate better, particularly the prefrontal cortex, which neuroscientist Kimberly Urban calls the brain's "boss". When noradrenaline and dopamine are present in the right amounts, the boss is an effective manager, explains Urban, who works at the Children's Hospital of Philadelphia. Too few neurotransmitters, and the boss is sluggish; too many, and it gets overwhelmed. The goal of treatments for ADHD and narcolepsy is to get the boss to the peak of function. Healthy users hope that they can raise their boss's peak.

People seeking a chemical boost do have legal options. "By far the most commonly used neurocognitive enhancers are nicotine and caffeine," says Peter Morgan, a psychiatrist at Yale University School of Medicine in New Haven, Connecticut. Instead of blocking reuptake, caffeine stimulates the release of extra noradrenaline and dopamine; its effects aren't as strong or as long-lasting as those provided by the other drugs. Nicotine mimics the neurotransmitter acetylcholine, which affects learning and memory. And no one bans people from pumping up their brains by smoking or drinking coffee during competitions or before an exam.

UNCLEAR BENEFITS

Researchers are attempting to quantify the effects of prescription neuroenhancers in healthy people. In one study, Stefano Sensi, a neurologist at G. d'Annunzio University of Chieti-Pescara in Italy, and his team asked 26 university students to take an intelligence test. They then gave each volunteer either a dose of modafinil or a placebo before re-administering the test³. For the test, called Raven's matrices, participants were required to complete the ninth pattern in a 3 × 3 geometric puzzle. They were scored on the number of grids that they answered correctly. Solving the puzzle requires quick and flexible thinking — called fluid intelligence.

Results were mixed and depended on the difficulty of the matrices. Modafinil made no difference on the easiest or the hardest puzzles. The drug did increase scores for the grids of medium difficulty, mostly for those who scored low in the pre-drug test; it made little difference to participants who nailed the matrices on their first try.

Sensi's work was among 24 papers included in a 2015 review of modafinil in healthy people⁴. The studies used a variety of cognitive tests, and the review found that, on average, modafinil did seem to help — particularly with decision-making, planning and fluid intelligence. The more complex the task, the more that modafinil helped. "On the basis of the evidence," says Battleday, "modafinil is improving people's performance." But the

"They don't really live up to the name smart pills"



Competition at the ESL tournament was intense.

results were not uniformly positive. Not every test showed benefits and, in a couple, the drug seems to have stunted creativity.

The review authors also noted that many cognitive tests had been designed to assess impairment, not enhancement. For example, people with a brain injury or dementia may struggle with a clock-drawing test, but someone with normal cognition will usually get it right — leaving no room for smart drugs to assist. Psychologists have few options to adequately measure cognition in healthy people, says review co-author Anna-Katharine Brem, a neuropsychologist at the University of Oxford, UK.

As with any mind-altering drug (caffeine and nicotine included) addiction or dependence are concerns. People who take drugs for ADHD do not seem to get hooked, says James McGough, a child and adolescent psychiatrist at the University of California, Los Angeles. However, he does not know if the same drugs might prove addictive in healthy people. After all, Adderall is an amphetamine, which has established addictive properties. Ritalin and modafinil seem to be less addictive, says Urban, but that does not mean that regular use is without risk. Morgan points out that regular use of coffee and cigarettes causes consumers' brains to adapt so that they need the stimulant just to function at their normal cognitive level. He suspects, the same might occur with smart drugs, even if users lack the compulsive craving that characterizes addiction.

As for long-term effects, nobody knows. Urban and colleagues' experiments in rats indicate that Ritalin could be bad for developing brains⁵. The researchers treated both adults and juveniles with one milligram per kilogram body weight, which is within the normal range for human treatment. In the grown-up rats, the drug increased nerve firing in their prefrontal cortex. But in the 15-day-old rats, equivalent to a preteen human, firing went down. If Urban stopped the drug, the effects went away. But when she tripled the dosage — equivalent to a high, but not unheard of, human prescription — the firing rates stayed low even 70 days after the treatment stopped.

The neurotransmitters that the medications

are known to target, noradrenaline and dopamine, are crucial regulators of brain maturation during puberty, Urban explains. Although the drugs don't seem to cause problems in teenagers with ADHD, they might throw off development of a healthy brain. She speculates that the poor firing patterns observed in the rats might translate to problems with working memory and flexible thinking in people. For example, someone might have a hard time finding a new route to work if their usual path is blocked. Indeed, she says, healthy children who take too much Ritalin can exhibit "extreme perseverance" — for example, being unable to pause a video game when it's time for dinner, persisting with one topic of conversation without being able to switch gears, or feeling emotions such as anger for a longer time than a situation warrants.

SMART MORAL COMPASS

Smart drugs are still primitive, Sensi says. They temporarily alter multiple neurotransmitters, so they aren't very specific. A better approach, he suggests, could be to develop drugs that would promote nerve-cell growth or the rewiring of the brain, inducing changes that would permanently enhance thinking.

However, the current medications are still potent enough to raise ethical questions. One such concern revolves around social equality. Not everyone has equal access to smart drugs, and there is a danger that only the privileged will be able to get ahead with amped-up cognitive powers. The result would be yet another force widening the gap between the haves and the have-nots, says Nita Farahany, a bioethicist at Duke University in Durham, North Carolina. Or, there might be a sort of arms race, with people taking ever more advanced smart drugs just to keep up. At her own institution, Farahany says, students were so worried about brain-boosters that the university amended its honour code in 2011 to state that "the unauthorized use of prescription medication to enhance academic performance" was a form of cheating.

For now, at least, even the scientists who study smart drugs aren't relying on them. Most of those interviewed for this article said that they stick to coffee, tea or energy drinks. Morgan, for his part, suggested that the same cognitive benefits can be achieved by simply taking a refreshing nap. ■

Amber Dance is a freelance science writer based in Los Angeles, California.

1. Singh, I., Bard, I. & Jackson, J. *PLoS ONE* **9**, e105969 (2014).
2. Franke, A. G. et al. *BMC Med.* **11**, 102 (2013).
3. Esposito, R. et al. *PLoS ONE* **8**, e69224 (2013).
4. Battleday, R. M. & Brem, A.-K. *Eur. Neuropsychopharmacol.* **25**, 1865–1881 (2015).
5. Urban, K. R., Waterhouse, B. D. & Gao, W.-J. *Biol. Psychiatry* **72**, 880–888 (2012).