

### *What Do I Do Now?*

particular scenario, I do not think I would prescribe a controlled substance such as the dopamine reuptake inhibitor modafinil (Provigil) or any of the amphetamines such as Adderall. (Piracetem is not available in the United States.)

The patient's request is not unusual. My younger colleagues inform me that Adderall, and other stimulants are used commonly in college and professional school to "get an edge" by using what is believed to be a cognitive enhancer. I believe that data support the use of these agents in patients who have been appropriately diagnosed within the spectrum of attention disorders. The evidence for improved performance in patients outside the attention-deficit/hyperactivity disorder (ADHD) spectrum is less convincing for me. Certainly, attention span is heightened and output is increased; however, the improved quality of that output, and retention of the "crammed" material, is more suspect. In short, I have concerns about the degree of benefit provided for someone without appropriate indications. I will accept that the risk in a healthy young individual, who has been screened for cardiac and psychiatric contraindications, is low, but not insignificant.

My reasons for not prescribing go beyond a low benefit/risk ratio. Ms. P. told her physician that her performance had been slipping in the past year. Even if I could produce a cognitive enhancer that would allow her to ace her final examination, it still would not allow her to learn all she missed in the previous year. I never went to law school; however, I suspect that there are some things taught in that last year that are important for a lawyer to know. My compliance with Ms. P.'s request would make me complicit in promoting an individual who may not be qualified for the job. It is true that she might obtain the drugs from another source, but she would not need, or have, my recommendation.

I am intrigued by Dr. Cefalo's ability to eliminate the diagnosis of ADHD "after some routine questioning." The diagnosis is not always so routine. I will entertain the possibility that Ms. P. actually does have ADHD. The benefit/risk ratio for giving drugs is now significantly better, and this would change my response, but not my decision to refuse the prescription as requested. Even if a stimulant such as Adderall were indicated, treatment is not a single dose therapy. Addressing the problem at the 11th hour is not the right way to receive an education. Ms. P.'s school has dealt successfully with patients with learning disorders before and most likely has a well-defined program for handling the issue. I would urge Ms. P. to seek the necessary diagnostic testing and, in consultation with her treating physician, approach the school for accommodations. The decision on the timing of Ms. P.'s graduation would no longer be in my hands; however, the appropriate medical management would remain there. In this situation, my professional obligation would be to aid, not to abet.

---

doi:10.1017/S0963180117000251

### **Commentary: Just Say "No"**

**Hervé Chneiweiss**

The answer to the question of whether Dr. Cefalo should prescribe modafinil or methylphenidate for his patient, is a simple "No" and the main reason is that physicians have the professional duty to prescribe on the basis of evidenced-based pathologies and treatments. Ms. P. does not present symptoms of attention-deficit disorder (ADD) (whether or not ADD should be considered a real disorder), and, in the limited reports that have appeared in the scientific

literature, so-called “cognitive enhancers” or “smart pills” do not improve cognitive performances in normal individuals.

Human beings have always attempted to improve their performance or their well-being. A few examples include: the process of learning, mastering the use of tools, and relying on the supporting help of substances such as coffee, alcohol, or hashish. The expression “cognitive enhancement” could give the impression that it describes an established phenomenon. However, the situation is more problematic in that there are questions and issues that need to be more thoroughly evaluated, as results cannot be considered self-evident.<sup>1</sup>

Moreover, the term reflects two entirely distinct situations. (1) It can describe modulation in the form of an increase of cerebral activity through biomedical techniques for patients affected by a neurological disease and/or deficit or handicap. Or, (2) it can refer to the use of such techniques by certain people whose health is in no way impaired. As a result, the concept covered by this expression includes the effects induced by such modulation and also the supposed intent to enhance.

The study of cognitive enhancement is fraught with considerable methodological difficulty, so that the results of the great number of inquiries and research efforts that have been undertaken on the subject must be approached with an open, but critical, mind, and with extreme caution.<sup>2</sup> Furthermore, the decision to “enhance oneself” is apparently the expression of the autonomy of a given individual; however, its underlying motivation and its consequences are essentially societal. The biomedical cognitive enhancement phenomenon can only be considered in relationship to a given sociocultural and economic context.

Considering the proposed case, the medical issues are numerous. A prime

concern for Dr. Cefalo will be “not to harm” his patient. Questions remain about the effects of “smart pills,” which may induce not only a poor enhancement but a real deterioration of cerebral function, in both the short and the long term. This is because the short-term studies address cognitive research and not neuroenhancement. Furthermore they are hindered by major methodological bias. Considering long-term data, there are none, because these treatments have only recently emerged, and neuroenhancement epidemiological follow-up studies are difficult to put in place.

If one considers the available studies, the major methodological difficulties are such that an interpretation of their results is at least questionable:

- Subjects are volunteers; usually male, young, and white, which necessarily introduces a selection bias;
- The numbers of subjects recruited are small, which can limit statistical power and validity;
- The mandatory experimental conditions as regards to diet, sleep, or coffee consumption do not reflect real-world situations;
- Most tests are conducted after a single dose of medication or a single brief focal stimulation, so that there is no way of knowing whether a benefit would be lasting after long-term repeated use;
- The studies are rarely double blinded and placebo controlled;
- Individual results vary with the cognitive performance baseline level, the metabolic characteristics of the substances being tested, the genotype of the enzymes involved, and the response to placebo;
- The studies are using a battery of tests with the risk that, in view of the great number of tests performed, finding a positive test result could be solely the result of chance.

## What Do I Do Now?

As to risks, some negative effects have been reported:

- A decreased improvement after methylphenidate administration with high cognitive baseline subjects<sup>3</sup>;
- Evidence of nonlinear (U-shaped) dose-response relationship, with no effects, or even detrimental effects with certain doses.<sup>4</sup>

Open questions remains regarding:

- The potential detrimental effect of a given enhancement on another brain function; for example, enhancement of working memory to the detriment of cognitive processing speed, and vice versa.<sup>5</sup> Could regularly taking methylphenidate when young lead to premature cognitive decline?
- The reversibility of adverse side effects
- Whether neuroplasticity; that is, the brain's capacity to modify its functional connectivity on a continuing basis—on which cognition, memory, and learning are founded—would be initially stimulated by neuroenhancement only to gradually fade away in the long run to the extent of arriving at an inversion of effects?<sup>6</sup>

Considering the poorly demonstrated positive effects along with real adverse ones, why do people who use neuroenhancement techniques hold such highly favorable opinions as to their effects? For example, 70% of methylphenidate users allege a positive or very positive effect, and the most frequent consumers are those whose satisfaction scores are highest. They do not hesitate to claim, in the media or over social networks, spectacular improvements in their intellectual performances. A Harvard student stated in *The Washington Post* that:

“In all honesty, I haven’t written a paper without Ritalin since my junior year in high school.”<sup>7</sup> The same discrepancy was also observed, for example, for Omega-3 polyunsaturated fatty acids supplementation, which, although perceived to be beneficial for cognition, have not been shown by double-blind studies and their meta-analysis to have produced any evidence whatsoever of enhanced cognitive test performance.<sup>8</sup>

Several theories have been put forward to explain the impact of the perceived individual benefit:

- The placebo effect with all its still mystifying characteristics;
- A ripple effect caused by the proximity of other enthusiastic users of “smart pills,” “study tools,” and “brain steroids”;
- A self-image enhancement effect, an illusion resulting from excessive self-confidence;
- An alertness effect in people who do not get enough sleep;
- Other pharmacological effects undetected by the tests used, but that might explain, for example, the fact that in a doubled-blind placebo/controlled study on amphetamines, subjects felt they were performing better when using amphetamines, whereas objectives results for all the tests were actually negative.

Finally, Dr. Cefalo may adopt a more general view considering public health. The ethical issue of autonomy is critically endangered by neuroenhancement. Individuals believe themselves to be free of any constraint, but they are driven by a compulsion to perform. “We must always be aware that the fervent quest for performance driven by an imperious desire to make progress, can mask the most constraining of alienations” (CCNE’s Opinion no. 121).<sup>9</sup>

The use of medication and of biomedical techniques raises the issue of a possible modification of the sense of self and of self-acceptance. Such use puts into question the permanent nature of individuals' relationships with themselves. What might be this "self" if we modify the manner in which we believe who we are? This should lead Dr. Cefalo to protect his patient from the deleterious influence of what she apparently learned on the Internet. By aiming to produce capability that is "above normal," cognitive enhancement axiomatically conveys distance from the duality of normality and pathology. The spectrum of applications is gradually being broadened and thereby disconnected from simply treatment of the pathological. But employing enhancements can also create new pathologies. It may be that in the near future, not being neuroenhanced will exacerbate a new kind of deprivation, and thereby create a novel form of addiction.

## Notes

1. Smith ME, Farah MJ. Are prescription stimulants 'smart pills'? The epidemiology and cognitive neuroscience of prescription stimulant

- use by normal healthy individuals. *Psychology Bulletin* 2011;137:717–41.
2. Repantis D, Schlattmann P, Laisney O, Heuser I. Modafinil and methylphenidate for neuroenhancement in healthy individuals: a systematic review. *Pharmacology Research* 2010;62:187–206.
3. Finke K, Dodds CM, Bublak P, Regenthal R, Baumann F, Manly T, et al. Effects of modafinil and methylphenidate on visual attention capacity: A TVA-based study. *Psychopharmacology (Berlin)* 2010;210:317–29.
4. de Jongh R, Bolt I, Schermer M, Olivier B. Botox for the brain: Enhancement of cognition, mood and pro-social behavior and blunting of unwanted memories. *Neuroscience and Biobehavioral Reviews* 2008;32:760–76.
5. Franke AG, Gränsmark P, Agricola A, Schühle K, Rommel T, Sebastian A, et al. Methylphenidate, modafinil, and caffeine for cognitive enhancement in chess: A double-blind, randomised controlled trial. *European Neuropsychopharmacology* 2017;27:248–60.
6. See note 4, de Jongh et al. 2008.
7. Outram SM. The use of methylphenidate among students: The future of enhancement? *Journal of Medical Ethics* 2010;36:198–202.
8. Luchtman DW, Song C. Cognitive enhancement by omega-3 fatty acids from childhood to old age: findings from animal and clinical studies. *Neuropharmacology* 2013;64:550–65.
9. Comité Consultatif National d'Éthique, 2013; available at <http://www.ccne-ethique.fr/fr/publications/reours-aux-techniques-biomedicales-en-vue-de-neuro-amelioration-chez-la-personne-non#WJZMIBApquU>