

HEADS UP Krishna Chinthapalli

The billion dollar business of being smart

Demand for cognitive enhancement is huge and growing

The prolific French novelist Honoré de Balzac wrote for 15 hours a day with the help of his “precious essence.” After a dose, he said, “Ideas march into motion like battalions . . . The cavalry of metaphor deploys with a magnificent gallop; the artillery of logic rushes up.”¹ He eventually took it up to 50 times a day. Caffeine was Balzac’s “smart drug.”

Caffeine is still the drug of choice for many college students in search of the same effects. Most have used coffee, caffeine drinks, or caffeine tablets to help them study.² In the United States, caffeine is now being supplanted by the prescription stimulants Adderall (amphetamine plus dextroamphetamine), methylphenidate, and modafinil. Some 5-15% of college and university students report taking these stimulants to help academic performance but most do so only occasionally (40% had used them only once or twice).³ Colleges with higher entry criteria have a higher prevalence of stimulant use. In high schools, too, 7% of final year students took a prescription stimulant without a prescription in 2014.⁴

The number of students using stimulants legally has also been increasing because these drugs are indicated in the treatment of attention deficit hyperactivity disorder (ADHD). One in nine US children has a diagnosis of ADHD, and the prevalence is increasing by 5% a year.⁵ Some of this increase may be due to malingering, with a quarter of college students thought to be feigning symptoms (for prescriptions or incentives such as extended time).⁶

The UK has fewer data, but a 2012 online survey of university students showed that lifetime prevalence of drug use to help academic performance was 24% for caffeine pills, 6% for modafinil, 4% for methylphenidate, and 2% for amphetamine.⁷ Two thirds of

remaining students said that lack of access was the only reason they had not tried such drugs.

Aside from stimulants, other tools purport to keep your brain sharp. Crosswords are being replaced by brain training games, now a billion dollar industry. Overstated claims by software companies led to a consensus statement last year by more than 60 neuroscientists warning that evidence was sparse and of poor quality. They concluded, “If an hour spent doing solo software drills is an hour not spent hiking, learning Italian, making a new recipe, or playing with your grandchildren, it may not be worth it.”⁸

Prescription drug manufacturers have been keen to take a slice of this market. Cephalon, which released modafinil in 1998 for narcolepsy, was marketing the drug for off-label uses such as fatigue or depression with little clinical support.⁹ It worked: 80% of modafinil prescriptions were for off-label use between 2001 and 2006, but it eventually also led to a \$425m (£275m) fine in 2008.¹⁰ This was the first time a drug company was prosecuted for promoting off-label uses that lacked scientific evidence. The company also extended the patent from 2001 by obtaining a patent on a specific formulation that ran until 2014. Generic companies could circumvent this new patent by creating different formulations, and four of them applied to do just that. In May 2015 the US Federal Trade Commission fined Cephalon \$1.2bn for unlawfully extending its monopoly by paying the generic companies \$300m to delay their generic drugs until 2012.¹¹ Meanwhile, modafinil sales were \$1bn a year.

Cephalon had a longer term plan, common in the drug industry, known as “product hopping.” Cephalon wanted to switch users from modafinil to its newer compound armodafinil, which has a patent until 2016, before generic modafinil became available



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in 2012. Armodafinil has a patent until 2016. To do this, it raised the price of modafinil tablets from \$5.50 to \$13.60 over five years until 2009 and introduced armodafinil at \$9 a tablet.¹²

Methylphenidate and amphetamine work by increasing extracellular dopamine levels, but the mechanism of action of modafinil is not fully understood. It may increase cortical levels of catecholamines, glutamate, and serotonin.¹³ Whatever its mechanism, modafinil has fewer side effects, particularly producing less dependence. A recent systematic review concluded that modafinil improves executive functions.¹⁴ However, 22 of the 24 studies considered only a single dose of modafinil for effects on cognitive tasks and side effects.

Banned in chess

“With Adderall, I’d characterize the effect as . . . correction of an underlying condition. Provigil [modafinil] feels like enhancement,” Paul Phillips, a professional poker player, told the *New Yorker*.¹⁵ Phillips won more prize money within six months of taking amphetamine than in the previous four years. Stimulants are allowed in poker tournaments but banned in chess.

In the competition for grades, Duke University in the US has banned stimulants, stating that “the unauthorized use of prescription medication to enhance academic performance” constitutes cheating.¹⁶ There has been little public debate about the ethics of powerful “smart drugs,” which may arrive soon owing to increasing consumer demand and increasing research into dementia treatments. For now we can still have a cup of coffee.

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NO HOLDS BARRED Margaret McCartney

Futile exercise

We're bossy and boring. Do more exercise! Take the stairs! Have you done your 30 minutes today? Exercise is promoted as a moral good, something to which responsible citizens should be enslaved, or at least devoted.

We are all urged to exercise regularly to save the NHS money in the long term, to stop us getting fat, getting diabetes, Alzheimer's disease, depression—and from infarcting our myocardiums. We are repeatedly told of a host of diseases that we might experience if we dare not clothe ourselves in Lycra and step up to the treadmill. In short, we are oppressed by medical do-gooders, nagging us to do more and guilt tripping us into going to the gym.

Doctors are not immune to this pressure. Cardiologists at a 2013 conference who dared to use an escalator rather than the stairs had their photographs shared on Twitter with disdain (<http://bit.ly/1EBXAtD>); in their defence, they probably had massive suitcases.

But, just as in general elections, the public doesn't like a negative campaign. Asking us to do something hard now for a possible absence

of diabetes in 20 years is a prime example. The medical establishment should not be in charge of promoting exercise, because we come across as stool gazing, risk averse killjoys, pointing fingers joylessly from a lectern.

Nagging people about the need to do exercise to achieve health won't work. Exercise should be for the people, by the people. It should be about good living—less “good for you” and more “feel good.” To run and work up a sweat results in a satisfying leg tingle for the rest of the day; the roaring pleasure of downhill on a bike is worth the thigh burn on the uphill. The truth is that post-exercise glow is on the orgasmic spectrum. And Zumba dance classes encourage friendships, just as walking groups create networks. Medicine should agitate to create a society in which exercise is the easy, pleasant option; we should quit nagging and start enabling.

Until people perceive it as safer to send their kids to school by bike or on foot rather than to drive them, we have failed. Children



We come across as stool gazing, risk averse killjoys, pointing fingers joylessly from a lectern

should be allowed to make the street they live in their playground (see the fantastic Playing Out project: <http://playingout.net>). We need streets designed for play and active travel. We need cities that love cycling and encourage rather than merely tolerate it, and local authorities should think imaginatively about how to offer affordable opportunities to people who lack the confidence or the means to join in.

It's not patients that doctors should be nagging—it's policy makers.

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BLOG Trish Groves

How research data sharing can save lives

Everyone's been missing a trick.

The whole debate on sharing clinical study data has focused on transparency, reproducibility, and completing the evidence base for treatments. Yet public health emergencies such as the Ebola and MERS outbreaks provide a vitally important reason for sharing study data, usually before publication or even before submission to a journal, and ideally in a public repository. Not just from randomised controlled trials, but from case series and samples, lab testing studies, surveillance studies, viral sequencing, genomic work, and other epidemiological observational studies too.

During the Ebola crisis, researchers couldn't or wouldn't share data. Recently WHO held a consultation meeting in Geneva to tackle this. One big reason for withholding data was the mostly unfounded fear of having subsequent papers rejected by journals. But researchers capturing vital information in the field and in coordinating centres were too busy to write and submit those papers, and thus much time was lost before vital information could be disseminated. Did people die because of the Ingelfinger rule against prior publication?



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There were also, of course, some commercial disincentives to early data sharing, with numerous competitors scrambling to test potential magic bullets. All on top of the usual logistical challenges.

Researchers have to share early data with WHO when absolutely required in a PHEIC (Public Health Emergency of International Importance, of which there have been only three so far—related to H1N1, polio, Ebola).

WHO then shares this information with member states. But authors' fears about the Ingelfinger rule prevent them and WHO from making these data public. WHO and all at the consultation meeting agree that this isn't nearly good enough. And, anyway, there are many other kinds of public health emergency, eg the Haiti earthquake, in which it would be

powerful to share study data quickly, widely, and sometimes publicly. This isn't only about infectious disease outbreaks.

The four editors at the meeting, including me, drafted a statement whose final version will be out in the final WHO report in a few weeks:

“It was unequivocally agreed by representatives from leading biomedical journals that public disclosure of important information of potential relevance to public health emergencies should not be delayed by publication timelines, and that pre-publication disclosure must not and will not prejudice journal publication. It was agreed that pre-publication information sharing should become the global norm in the context of public health emergencies. Researchers should take the responsibility to ensure that results—even when preliminary—are adequately robust and have undergone quality control, prior to public disclosure to enable an evidence-based dialogue with the media and communities.”

This may all seem a no-brainer, but the Ebola crisis has made it clear that there's much unnecessary confusion and reticence out there.

Trish Groves is head of research, *The BMJ*

Multidisciplinary team meetings encourage overuse

Suboptimal decisions could be minimised by always including an advocate of the patient, writes **Franz Eigenmann**

In oncology, multidisciplinary team meetings (MDTs) or “tumour boards” are held to review cases of patients with cancer and to make decisions about treatment. A typical meeting might include medical oncologists, radiotherapists, surgeons, pathologists, and representatives of other medical specialties depending on the type of tumour, together with several junior doctors.

When I first attended these meetings 25 years ago, I was enthusiastic about their value. Discussing difficult cases in this way was helpful and offered some protection against the ad hoc decision making that can occur in medicine.

But the situation has changed. Today, the general feeling in many countries seems to be that treatment should be determined by an MDT meeting at every major decision point, for every cancer case (I hesitate to use the word “patient” because practice has become quite impersonal). More and more guidelines strongly advise this.¹⁻³

So, my enthusiasm for these meetings has gradually waned over the years. Yes: reviewing difficult situations in this way is efficient, but to have many staff spend time discussing clear cut

indications is a waste of resources. More importantly, the real decision makers in these meetings tend to be only the most senior doctors. Crucial decisions, therefore, are often made without doing the most important thing in medicine—seeing the patient. This is not acceptable.

Collective decision making

Collective decision making is known to reduce the sense of individual responsibility and to encourage riskier decisions.⁴ Many common treatments in advanced cancer are toxic and of marginal efficacy. Under these circumstances, decisions made collectively at MDT meetings may be biased towards recommending aggressive therapies that have little positive effect but cause patients misery.

The term “preferred treatment,” used by oncologists and drug companies, may also encourage poor decision making. Consider the treatment FOLFIRINOX, which comprises folinic acid, fluorouracil, irinotecan, and oxaliplatin. This chemotherapy regimen is described as the “preferred treatment”^{2,3} for pancreatic cancer after showing only marginal, albeit statistically significant, benefits in only a single trial. A participant in the MDT meeting would need a lot of courage



POSED BY MODELS MB/ALAMY

“Many doctors, nurses, and patients think that decisions taken in multidisciplinary team meetings are the law: obey, or face the consequences”

to state that he or she would prefer the patient not to get the “preferred treatment.”

The little research that exists shows that MDT meetings increase adherence to guidelines.^{5,6} Whether this is a good thing remains to be proved and depends on the wisdom of the guidelines themselves and their interpretation.

Many doctors, nurses, and patients think that decisions taken in MDT meetings are the law: obey, or face the consequences. While this misconception stands, patients and professionals have much to lose.

How might these concerns be tackled? The report of every meeting should explicitly state who made the final decision

and who is responsible for it. It should go without saying that this responsibility can be held only by someone who has seen the patient.

The meeting should always include an advocate of the patient—the patient’s GP or a hospital generalist, for example. This advocate could help patients to integrate their attitudes and preferences into the decision making process. And the opinion of the patient, through his or her advocate, should carry the same weight as that of the specialists.

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PATIENT COMMENTARY

Consider the person alongside the pathology

My experience of being discussed at multidisciplinary team (MDT) meetings backs Eigenmann’s view that someone who can present the patient’s perspective should be there.¹ It also suggests that patients should be alerted to these meetings and might value the option to represent themselves.

As a three operation, 11 year survivor of metastatic adrenal cancer,² I knew that it was likely to come back again one day. I dreaded annual scans and happily agreed to forgo them two years ago. This year, during reappraisal of my hyperparathyroidism, recurrence was detected.

The senior registrar broke the bad news gently by phone and mentioned that my case was due to be discussed at an MDT meeting. I asked whether I might be allowed to attend and be sent a copy of the scan results in advance. The consultant kindly agreed.

I sat at the back of the room, looking at my scans on the screens, listening to the thoughtful discussion between radiologists, oncologists, and endocrinologists, and taking in their views of the findings and possible management options. Nothing that they said came as a surprise. Few patients live with cancer this long without doing their own research, and I found it very helpful to understand the rationale for their conclusions.

Their professionalism impressed and reassured me. So did their courtesy

I was able to respond to questions and supply missing factual information about previous treatments

towards me—conveyed largely by their demeanour, for I was primarily there as a spectator, not as a participant.

I’m not sure what they felt about having me there, but it gave them insight into how well I am, and I was able to respond to questions and supply missing factual information about previous treatments in different hospitals.

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