SCIENCE AND SOCIETY

# ‘Smart Drugs’: do they work? Are they ethical? Will they be legal?

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Beyond pharmacological approaches to the treatment of memory loss that results from Alzheimer’s disease or stroke, there lies a broad diagnostic penumbra of ‘age-associated memory impairment’. New research that offers to attain the ancient goal of improving our cognitive ability raises an important issue — the use, by healthy people, of such pharmacological tools as cognitive enhancers. Here, I review the history and effectiveness of such supposed ‘nootropics’, and the ethical, social and legal issues raised by their potential use in disease and in the enhancement of ‘normal’ cognition.

Attempts to enhance human potential and performance are age old; magic potions to produce immortality, superhuman strength, potency and wisdom feature in the myths of most cultures. In the Western tradition, they run from the ancient Greeks to the contemporary cartoon characters of Asterix and Obelix. The shelves of health-food stores groan with pills that offer to improve everything from children’s IQ scores to memory in old age. A quick scan of the Internet offers an even wider range of both approved and non-approved drugs. Many are reportedly available over the counter at a variety of ‘smart bars’ across the west coast of the United States. While pharmaceutical companies race to provide potential treatments for memory loss in Alzheimer’s disease (AD), there are wider concerns about ‘age-associated memory impairment’, which supposedly affects the majority of the population over fifty years of age. Start-up biotech companies promise the imminent arrival of drugs that will prevent such an impairment, describing them as ‘Viagra for the brain’[1], and certainly functioning as Viagra for share values. And when Tang *et al.*[2] reported that increasing the number of NR2 NMDA (*N*-methyl-D-aspartate) receptors in the mouse hippocampus improved performance in the Morris water maze (a test of spatial memory), the paper attracted massive international publicity owing to the suggestion that the “genetic enhancement of mental and cognitive attributes such as intelligence and memory in mammals is possible”.

Such reports tend to replace ‘memory enhancement’ with a more general ‘cognitive enhancement’ — a cloudy issue that I discuss below in more detail. However, the suggestion that it might be possible to produce drugs with a ‘purely’ cognitive effect dates back to the work of Giurgea, who coined the term ‘nootropic’ in the 1970s to describe their function[3]. The term is derived from the Greek *noos* for ‘mind’, and *tropein*, meaning ‘towards’. Sara[4] quotes the following translation of Giurgea’s vision:

> “…do we realise as individuals or as a species, all of our genetic potential? … A pharmacological intervention is more and more feasible and acceptable at all levels of interface between genome and environment. This is the target of the Nootrope endeavour. These drugs, devoid of toxicity or secondary effects, represent a means to enhance plasticity of those neuronal processes directly related to the ‘Noosphere’ … Pharmacology can participate, very modestly, in one of the major efforts of humanity, which is to go beyond the Platonic question ‘Who are we?’ … Man is not going to wait passively for millions of years before evolution offers him a better brain … To develop a pharmacology of integrative action of the brain, in the nootropic sense, seems to me to have a place in this far-reaching human objective.”

More prosaically, Dean and Morgenthaler, in a book entitled *Smart Drugs and Nutrients* and subtitled “how to improve your memory and increase your intelligence using the latest discoveries in neuroscience”[5], argued that:

> “The concept of a fixed intelligence is … untrue … more and more business people and scholars are looking for the kind of ‘edge’ that athletes get from science … Research also shows that you may increase your intelligence by taking certain substances that have recently been shown to improve learning, memory and concentration … for improved exam-taking ability, better job performance and increased productivity [as well as] … delaying age-related intelligence decrease.”

Here, I review the evidence on which such claims are based, before turning to some of the ethical, legal and social issues that the potential of such agents might raise.

## Why enhance cognition?

Our personal memories — the autobiographical record — are in many ways what define each of us as individuals. And in an increasingly skills-driven and socially interactive world, memory — individual or technologically enhanced — is one of the keys to success. This is perhaps why loss of memory — an inability to remember — is so mysterious and frightening a condition. There are many disease states that are characterized by impaired memory and cognition. Some are genetic — for example, Down’s syndrome. Some are associated with accidental brain damage (such as the much studied amnesic patients with

hippocampal or temporal lobe damage), with stroke or with the vitamin deficiencies that result from alcoholism (Korsakoff's syndrome). Above all, there are the broad groups of senile dementias such as AD and Lewy body diseases. As the incidence of these disorders increases with age, and the age profile of populations in the industrial world is shifting steadily upward, there is a strong medical and social drive for research to develop neuroprotection strategies, or at least to reduce the rate and degree of decline. 'Solving' AD has become an important target for academic institutions and the pharmaceutical industry. But in addition to such relatively clearcut conditions (although clouded in diagnostic uncertainty until post mortem), there are those of us who fret over our inability to recall names or past events, and who are concerned about whether indeed we might be about to suffer from some form of age-associated memory impairment. And beyond this, is everyone else seeking that competitive 'edge' referred to by Dean and Morgenthaler[5].

Few would doubt the value of neuroprotection or amelioration of the effects of stroke or AD. But outside this lies the murky area in which 'normality' itself becomes a medical condition. Some features of cognitive function — notably, speed of processing — seem to decline progressively with age. As one ages, more trials are required to acquire simple conditioned reflexes, such as an eye blink in response to a light or tone. But given enough time and trials, the reflex can be acquired and little seems to distinguish the final performance of people on the grounds of age alone[6]. Old people often acquire better strategies for solving problems than young people, and in a less speed-obsessed age, this could be thought of as wisdom. Feelings of fading memory might often be associated more with depression[7]. So, targeting 'memory' *per se* might not be an appropriate strategy. The deficits associated with AD and other conditions relate to specific biochemical or physiological lesions. There is therefore no *a priori* reason — irrespective of ethical concerns or any other arguments — to suppose that, in the absence of pathology, pharmacological enhancement of such processes will necessarily enhance memory or cognition, which might already be 'set' at psychologically optimal levels. If they are suboptimal, this might reflect not a pharmacological deficit, but other social or personal life-history reasons. This is not to minimize the distress that most of us feel in our daily life as a consequence of lapses of memory. And, as politicians, card sharps and competitors for the *Guinness Book of Records* know, pharmacological intervention is not the only route to overcoming such problems. Memory — for names, hands of cards dealt, or even recalling $\pi$ to hundreds of decimal places — can be trained using non-pharmacological techniques that date back to antiquity[8,9].

In this context, it is worth querying the assumption that a perfect long-term memory is desirable. The psychological mechanisms of perceptual filtering, and of short-term, recognition and working memory, are clearly beneficial in blocking the accumulation of irrelevant or transiently required information in longer-term stores. The wisdom of the psychotherapeutic 'recovery' of past traumatic memories has been questioned in the context, for example, of psychoanalysis, and even the veracity of such apparent memories has been challenged in the context of 'false memory syndrome'[10,11]. The literature is full of anecdotal accounts of the problems faced by those few people who are apparently unable to use forgetting mechanisms to assimilate necessary and discard unwanted information. The most famous case is that of Shereshevkii, the patient who was studied over many years by the neuropsychologist Alexander Luria[12]. Shereshevkii was a synaesthetist with an apparently inexhaustible memory, recalling not merely complex nonsense formulae, but also the exact context in which he learnt them. His inability to forget made it impossible for him to hold down a career other than as a memory performer. His case poignantly echoes that of Funes, the 'memorious' — the fictional character created by the novelist Jorge Luis Borges:

> "…[Funes] remembered the shapes of the clouds in the south at dawn on the 30th of April of 1882, and he could compare them in his recollection with the marbled grain in the design of a leather-bound book which he had seen only once, and with the lines in the spray which an oar raised in the Rio Negro on the eve of the battle of the Quebracho … These recollections were not simple; each visual image was linked to muscular sensations, thermal sensations. … He told me: I have more memories in myself alone than all men have had since the world was a world … my memory sir, is like a garbage disposal…"[13]

It is no accident that, in the story, Funes dies young — of an overdose of memory, so to speak.

## Nootropes, remembering and forgetting

The implication of Giurgea's nootropic concept is that there are brain processes that are concerned with 'pure' cognition, memory formation or retrieval, and that drugs can be developed to affect these processes without peripheral or other central effects. Both propositions are questionable.

Memory formation requires — among other cerebral processes — perception, attention and arousal. All engage both peripheral (hormonal) and central mechanisms. Although the processes that are involved in recall are less well studied, it is safe to assume that remembering places similar demands on the brain. So, agents that affect any of these processes might also function to enhance (or inhibit) cognitive performance.

Memory formation in simple learning tasks is affected by plasma steroid levels[14], adrenaline[15] and even glucose[16]. At least one agent that has been claimed to function as a nootropic and was once widely touted as a smart drug — piracetam[17] — seems to act, at least in part, through the modulation of peripheral steroid levels[18]. Central processes can also affect performance by reducing anxiety, enhancing attention or increasing the salience of the experience to be learnt and remembered. Amphetamines, methylphenidate (Ritalin), antidepressants and anxiolytics probably act in this way[19]. Other agents that are regularly cited as potential smart drugs, such as adrenocorticotropic hormone (ACTH) and vasopressin[20], might function in a similar fashion. Last, there is evidence from animal studies that endogenous cerebral neuromodulators, including neurosteroids (for example, dehydroepiandrosterone[21]) and growth factors (such as brain-derived neurotrophic factor[22]), will enhance long-term memory for weakly acquired stimuli. The claimed neuroprotective effect of oestrogen, as evidenced by the lower incidence of AD in post-menopausal women taking hormone replacements[23], is still awaiting epidemiological verification; if proven, it might be that this effect is mediated through interconversions with neurosteroids.

## Approaches to enhancement

The lay literature, health-food stores and Internet sites propose lecithin and a variety of multivitamins — notably, the B complex and vitamin C — as neuroprotective, along with herbal extracts of ginseng, ginkgo biloba and other substances derived from non-Western, non-allopathic traditions as cognition and memory improvers (BOX 1).

More allopathic approaches to enhancement have tended to follow clinical fashion in identifying the physiological or biochemical processes that are impaired in cognitive deficit and focusing on ameliorating them. Suggestions that one of the main problems of cognition in ageing lay in deficits in general

**Box 1 | Some alleged 'smart drugs' and cognitive enhancers**

**Agents once supposed to act through glutamatergic mechanisms**
Piracetam | Aniracetam | Nefiracetam | Oxiracetam | Pramiracetam | Fipexide | Pyroglutamate

**Glutamatergic agents under clinical trial**
Ampakine | Memantine

**Agents that affect GABA (γ-aminobutyric acid) function**
$GABA_B$ receptor antagonist CGP 36742 | Methylphenidate (Ritalin)

**Serotonergic agents**
Ondansetron

**Cholinergic agents (licensed for Alzheimer's disease)**
Galantamine | Rivastigmine | Donepazil

**Adrenergic agents**
Adrenaline

**Agents that act on cerebral circulation or calcium homeostasis**
Vinpocetine | Hydergine | Phenytoin | Nifedipine | Nimodipine | Idebenone

**Hormones and neurohormones**
Dehydroepiandrosterone (DHEA), DHEA-sulphate | Vasopressin | Adrenocorticotropic hormone

**Miscellaneous others**
Acetyl-L-carnitine | Choline | Lecithin | Gingko biloba | Ginseng | Antioxidants | B, C and E vitamins | Nicotinic acid, xanthinol nicotinate | Orotic acid | D-Cycloserine

cerebral metabolism provided the impetus for nootropics that were supposed to boost the circulation and use of oxygen. The findings that cholinergic cells are among the first to die in AD, and that cholinergic mechanisms could be involved in memory formation, led to the search for potential cholinomimetics. More recent evidence on the involvement of GABA (γ-aminobutyric acid)- and glutamate-mediated processes has shifted the focus of research once more.

Various prescription drugs enhance cerebral metabolism and have been proposed as potential nootropics. An example is co-dergocrine mesilate (Hydergine), an anti-hypertensive ergot extract that is claimed by Dean and Morgenthaler to "increase intelligence, memory, learning and recall" among a dazzling array of other virtues[5]. The *British National Formulary*, by contrast, states that "the drugs have not been shown clinically to be of much benefit"[24]. A more solid approach followed the hypothesis that cerebral metabolism was affected by changes in calcium homeostasis during ageing[25]. Data from several animal models indicated that L-type calcium channel blockers, such as nimodipine and nifedipine, enhance memory acquisition, especially in aged animals[26]. However, as with many other attempts to apply the findings of pharmacological intervention in animal learning to clinical use, trials of these drugs in humans have proved to be ineffective at enhancing learning or memory.

The cholinergic hypothesis for the memory deficits associated with AD led to an intensive search for drugs that might restore cholinergic function. Again, animal models pointed the way. A routine procedure has been to block cholinergic function with scopolamine, and then to test agents that might restore learning or retention. Several candidate drugs were identified in this way. However, most proved to be ineffective at ameliorating the deficits of AD in humans, still less as general memory or cognition enhancers[27]. This is not really surprising, as the logic of the animal experiments was essentially circular: scopolamine produces learning deficits, so agents that block or reverse scopolamine activity prevent these deficits (although the cholinesterase inhibitor physostigmine is reported to enhance the selectivity of perceptual processing during working memory in young volunteers[28]). However, unless the memory deficit in humans is indeed caused by a scopolamine-like blockade of cholinergic function, it is not likely to respond in the same way. Tacrine, an early cholinesterase blocker that was reported to have some alleviating effects, was effective only in a minority of cases and often produced severe adverse reactions. Two drugs licensed in the United Kingdom, donepazil (Aricept) and galantamine (Reminyl), are reversible inhibitors of acetylcholinesterase; another, rivastigmine (Exelon), is a reversible, non-competitive inhibitor. All of them can produce unpleasant adverse reactions and are only mildly efficacious in a proportion of patients. Although it is hard to imagine their more general use as treatments for age-associated memory impairment (or as nootropics in the Giurgea sense), they are apparently under trial[1].

Recent advances in elucidating the molecular cascade that is involved in memory formation in animal models (for reviews, see REFS 29,30) have implicated glutamatergic mechanisms, and especially the NMDA receptor complex, as being crucially involved in the initial stages of acquisition in many learning tasks. Evidence of interactions between cholinergic and glutamatergic processes also points to these as possible sites of intervention. Even before the current research era, it was suggested that the acetams (such as piracetam, aniracetam and oxiracetam) might work through glutamatergic mechanisms[31], and pyroglutamate (2-oxo-pyrrolidone carboxylic acid) features in the smart-drug catalogues for the same reasons[32,33]. Mondadori's demonstration that the acetams act peripherally by enhancing corticosteroid release[18] has not entirely ruled out the possibility of a central effect. However, the evidence for its effectiveness in humans is slight. The report that increasing the numbers of hippocampal NR2 receptors improves the performance of mice in the Morris water maze[2] has drawn further attention to the potential role of NMDA receptors as effective sites of intervention for cognitive enhancement.

Animal models of memory formation indicate that synaptic events are followed by an intracellular cascade that involves calcium fluxes, a variety of protein kinases, and activation of transcription factors and immediate early genes such as c-*Fos*, c-*Jun* and *Zif-268* (REFS 29,30). An important step in this sequence involves the cyclic-AMP-responsive-element-binding protein (CREB), which has been implicated in memory formation in both *Drosophila*[34] and mice[35]. At least two companies have been set up to explore the role of CREB as a key site of potential smart-drug action[1], although it should be pointed out that, even in animal models, the role of CREB in retention seems to depend rather sensitively on the training protocols that are used[36].

The ability of these interventions to enhance human memory remains speculative at present. But this illustrates a more general issue: the relevance of animal models in the field of memory and cognition. It is striking that, despite clearcut evidence that a variety of agents — the acetams, L-type calcium channel blockers, glutamatergic and cholinergic agonists — can enhance memory-related performance in animals, they have generally proved to be disappointing when taken to clinical trial in treating cognitive decline and dementia.

There are several possible reasons for this. One is that the biochemical specificity of the processes that lead to decline in humans might differ from the effects of pharmacological manipulation in animal models. Perhaps more importantly, assumptions about the similarity of human memory to animal models of learning and recall (which must always be tested by the criterion of performance of some task, whether it be maze navigation or the expression of preference) might be false. Animal models cannot reprise the subtleties of human verbal, recognition and autobiographical memory. General 'cognition' is hard to test in animal models (except perhaps in complex tasks with primates), and memory is but one aspect of cognition in humans.

### Do we want cognitive enhancement?

It might seem *a priori* self-evident that protection against cognitive impairment and the recovery of cognitive functions in the absence of proactive treatment, if possible, are desirable. But to "give a 70-year old the memory of a 20-year old", as the claim for one of the potential enhancers has put it, requires a little more discussion before nodding and passing on to the wider issues. Memory loss confounds at least two distinct phenomena. In lay discussion, it generally implies loss of long-term episodic, semantic and autobiographical memory, arguably the feature of patients with AD that is most distressing to carers. Drug treatment is conceived of as aiding in the recovery of these lost memories, but there is no indication that any of the agents under discussion as putative cognitive enhancers or for therapeutic intervention in AD will achieve this. Rather, they might serve to prevent loss of short-term memory for recent events — that is, to aid in the transition between short- and long-term memory (although more effectively, it is to be hoped, than the current, relatively ineffective generation of anticholinesterases). As forgetfulness for recent events (Did I do the shopping? Where did I leave my keys?) is one of the characteristic features of the earlier stages of AD, the newer generation of enhancers, including those that reverse some of the specific biochemical lesions, could function to alleviate these early features, enabling those suffering from AD to remain independent for longer. It is improbable that they will reverse or prevent the progression of the disease (unlike the hopes surrounding the recent vaccination trials[37]). And if an agent could be developed that did awaken long-dormant or even erased memories in patients in the advanced stages of the disease, they might not necessarily be welcome, as such re-awakenings might be as painful as those documented by Sacks[38] in the context of the use of L-DOPA (L-3,4-dihydroxyphenylalanine).

Neuroprotection would seem to be a better strategy. But once again, it is not an unequivocal good. Some of the genetic and environmental risk factors for AD are understood, but almost all (other perhaps than the small percentage of familial early-onset AD cases) are at best only weakly predictive. One would have to weigh carefully the risks and costs of long-term medication, and the penumbras of its perhaps inappropriate use by the so-called 'worried well', concerned about failing memory and the peculiar diagnosis of age-associated memory impairment. As a society, we are becoming familiar with long-term preventive medication — for example, with the use of antihypertensives and statins to reduce the risk of coronary heart disease for those who are judged vulnerable. However, the assessment of risk factors and weighing of inevitable adverse and unwanted drug effects are tricky even in physiological and biochemical contexts that are better understood than cognition. Growing old is not a disease but a condition of life, and one can question the consequences of creating a society that refuses to accept ageing — at least for the wealthy. However, it is beyond dispute that both social and pharmacological measures that approach the WHO (World Health Organization) goal of 'adding life to years' are to be welcomed.

Beyond these potential clinical and neuroprotective uses for the cognitive enhancers is the terrain that raises most ethical and legal concern — their potential for improving, as Dean and Morgenthaler put it[5], school and examination performance and competitive edge. Is such enhancement theoretically possible? Despite the problems that those of us with 'weak memories' experience in our daily life, more does not necessarily mean better. So, even if a pharmacological remedy for deficits such as those in AD were developed, this would not automatically mean that a supernormal level of the relevant molecule would produce supernormal performance. Think of the classical inverted 'U' for the effects of steroids, for example. Where brain processes depend on a subtle balance between neuromodulators, neurotransmitters and their multiple receptors, simply adding more of one (such as an NMDA receptor) might be more disruptive than beneficial.

Even if this proved not to be the case, and safe and effective enhancers of 'normality' could be produced, there is a fine medical and ethical line between correcting deficits and improving on 'normality', as has been extensively discussed in the context of the potential for human genetic manipulation (see, for example, the recent Nuffield report[39]). The issues are analogous to those raised by the uses of steroids and other performance enhancers in athletics, where a sort of arms race has developed between the athletes who might use them, and the rule makers and enforcement systems that detect and ban them. But we should not be naive. Generations of students (to say nothing of creative artists or dealers in frenetic stock markets) have used such stimulants as have been available — caffeine, alcohol, amphetamines — to sharpen concentration as they revise for and sit examinations. Would the availability of genuinely effective new drugs make any difference in principle? Perhaps not, but one can foresee interesting legal issues arising if the losers in some competitive examination cry foul and seek redress. The clutch of insurance and related cases that surround the use of Prozac, especially in the United States[40], are a foretaste of what might arise in this new context. The truth is that social thinking and policy on the uses of chemicals that affect brain or body performance are hopelessly confused. Some are legal and purchasable over the counter (alcohol, nicotine), others are on the verge of at least decriminalization (cannabis), some are acceptable in general but not in competitive situations (steroids), some are available only on prescription or deviously through the Internet (Viagra, Ritalin), and some are illegal (ecstasy, heroin). Within the foreseeable future, cognitive enhancers — or agents that are claimed to function as cognitive enhancers, whether or not they are genuinely effective — are set to join this eclectic set.

My best guess is that, as with steroids for athletes, they will turn out to be virtually uncontrollable legally, and as a society, we are going to have to learn to live with them[41]. But some forms of regulation will be needed, and these can best be achieved by some sort of democratic consensus, perhaps by way of discussions in the varying forms of citizen's juries and technology forums that many European countries have been experimenting with in the context of developments in genetics. But it is important that we try to be proactive in advance of the technological development, rather than constantly trying to close already open stable doors. And perhaps we ought to begin by asking a different question: what is it about the way we live today in advanced industrial societies that drives people to seek pharmacological fixes? Should we be spending less time looking to adjust our minds, and more in adjusting society instead?[42]

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## Online links

DATABASES
The following terms in this article are linked online to:
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brain-derived neurotrophic factor | c-*Fos* | c-*Jun* | CREB | L-type calcium channels | NMDA receptors | vasopressin | *Zif-268*
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OPINION

# Claude Bernard's *Des Fonctions du Cerveau*: an *ante litteram* manifesto of the neurosciences?

*Fiorenzo Conti*

Claude Bernard, whose insights drove the progress in the life sciences that took place in the nineteenth century, devoted a considerable part of his research to neurological studies. In 1872, Bernard wrote an essay entitled *Des Fonctions du Cerveau*. Because of its modern tone and its emphasis on equating brain functions to those of other organs, this work can be regarded as an *ante litteram* manifesto of the neurosciences.

Together with Johannes Müller (1801–1858) and Carl Ludwig (1816–1895), Claude Bernard — who was born in Saint-Julien de Villefranche on 12 July 1813, and died in Paris on 11 February 1878 — is considered to be the father of modern physiology (FIG. 1). In his renowned *Introduction à l'Etude de la Médecine Expérimentale*[1] of 1865, Bernard succeeded in ordering decades of experimentation and theoretical analysis of the life sciences, and became one of the best-known scientific figures of the second half of the nineteenth century[2–6]. Even though Bernard has been the subject of an impressive number of studies and monographs, his neurological studies have been largely neglected. Here, after a brief overview of Bernard's neurological work, I shall focus on a little-known but extraordinarily modern essay entitled *Des Fonctions du Cerveau*, which anticipates the *credo* of modern neurosciences.

### Bernard's neurological studies

Of Bernard's 186 scientific publications reported by Malloizel[7], 60 focus on the nervous system. If those on fever and anaesthesia are included, this proportion reaches 50%. Of these, the vast majority, which form part of the *Leçons sur la Physiologie et la Pathologie du Système Nerveux*[8] (FIG. 2), study the cranial nerves and visceral innervation. Many are studies of the toxicological properties of neuroactive compounds, such as curare, curarine, opium, atropine, strychnine and nicotine; these are collected in the *Leçons sur les Effets des Substances Toxiques et Medicamenteuses*[9].

The bulk of Bernard's early neurological studies were profoundly influenced by François Magendie (1783–1855), both