Drug development: attitudes and beliefs

Pills to make you smarter

The use of brain-boosting drugs that enhance thinking and learning is growing

If you could take a drug to boost your brainpower, would you? This question is one facing students all over the world. In a 2016 study of medical students from two Lithuanian universities, over 8 per cent of the 572 students surveyed said they had taken cognitive enhancers, mostly to help with their studies.

A more recent survey suggests use is growing and not just among students. According to data from the Global Drug Survey, in the US, the number of people who say they have used drugs for cognitive enhancement rose from 20 to 30 per cent between 2015-2017. Meanwhile, in the UK, although use is less widespread, it is rising faster – use increased from 5 to 23 per cent over the same period.

The mind-enhancing drugs include illegal stimulants such as cocaine and medications prescribed for people with attention deficit hyperactivity disorder (ADHD) or sleep problems. Whilst a few people use their own prescriptions, most are using drugs they get from friends, family members, or dealers. About 10 per cent are bought online.

Performance-enhancing substances are nothing new. Long-haul lorry drivers and aircraft pilots are known to pop amphetamines to stay alert and university students down energy drinks to ward off drowsiness during all-nighters. These rev up the entire nervous system but only have a temporary effect.

Newer cognitive enhancers can improve mental functions in a lasting way. Modafinil (marketed as Provigil) is a treatment for narcolepsy and other sleep disorders that has proved popular among students who want to enhance their mental prowess. In the UK, it is only licensed for medical use. In 2016, the Medicines and Healthcare products Regulatory Agency (MHRA) clamped down on illegal and online sales of the drug, seizing 31,000 doses.

Another is methylphenidate, better known as Ritalin, the drug used to treat attention deficit ADHD. In the US, where ADHD is more commonly medicated, the central nervous system stimulant Adderall – a combination of amphetamines – is used to treat the disorder and thus is more widely used for cognitive enhancement than in the UK, where amphetamines are illegal.

Whilst none of these drugs are approved for use in healthy individuals, more and more people are taking them to gain a mental edge. Modafinil, when given to adults playing games specially designed to test mental skills, has been shown to increase cognitive agility, by increasing alertness and the ability to concentrate on a task. Meanwhile, some parents use the Ritalin prescribed to their children and some academics take these drugs regularly to enhance their memory and concentration.

Such ‘smart drugs’ remain a hot topic. If a drug can improve an individual’s performance, and they happen not to experience any side-effects, some argue that it can’t be such a bad thing. What’s the difference between a can of caffeine-containing Red Bull and a hike from modafinil? On the other hand, would it be right for pushy parents to start giving mind-enhancing pills to their children? As the drugs don’t actually make people brainier – the effects wear off when the drug stops working - educational success depends on being able to access the drugs consistently, encouraging long-term use.

No major studies have been conducted on the long-term effects of using these drugs for cognitive enhancement. However, side effects of modafinil, for example, can include chest pains, anxiety and nausea. The MHRA has warned students not to put their health at risk by self-medicating, suggesting some cognitive enhancers could cause psychosis.

Memory-blockers

So what about the flip side: a drug to erase bad memories? It may have failed Jim Carrey in *Eternal Sunshine of the Spotless Mind*, but neuroscientists have now discovered an amnesia drug that can dull the pain of traumatic events. The drug, propanolol, was originally used to treat high blood pressure and heart disease. But doctors noticed that patients given the drug suffered fewer signs of stress when recalling a trauma.

Starting in the 1990s, scientists found that the drug can disrupt the way memories are stored. This ability could be invaluable in treating trauma victims to prevent associated stress disorders. In 2016, a psychologist at McGill University in Canada announced plans to begin treating victims of the 2015 Paris terror attacks with propanolol. But research on the drug has also triggered suggestions that licensing these memory-blocking drugs may lead to healthy people using them to erase memories of awkward conversations or embarrassing blunders.

It may seem tempting to use a drug to prevent a painful experience becoming an unwanted memory. But how would that affect our development as individuals? Bad experiences help make us what we are. We learn from them. They help us avoid repeating mistakes.

And there are other uses that may make us uncomfortable. The military is interested in modafinil as a drug to maintain combat alertness. A drug such as propranolol could be used to protect soldiers from the horrors of war. That could be considered a good thing – post-traumatic stress disorder is common in soldiers. But the notion of troops being unaffected by their experiences makes many feel uneasy.

Prevention: still better than a cure?

To what lengths should we go to prevent disease?

What would you say if you heard that drugs were being pumped into the water supply? Would it horrify you? In fact, it has been going on for decades, with fluoride. Nearly six million people in the UK currently drink tap water spiked with fluoride.

When fluoridation began in 1945, in Grand Rapids, Michigan, it was hailed as a harmless chemical to prevent tooth decay. But the practice has had its critics, who claim fluoride can cause a range of health problems – from tooth mottling to cancer.

Governments back water fluoridation as a cost-effective way to tackle tooth decay. Reports by the UK and New Zealand governments published in 2014 found that there was no difference between rates of cancer in areas where water is fluorinated and areas where it is not. However, some people feel it should be a matter of choice. Fluoride can also be obtained easily from toothpaste.

Plans to make people eat folic acid by adding it to bread have also ignited controversy. In 2006 and again in 2009, the UK government's Scientific Advisory Committee on Nutrition (SACN) proposed that all white flour be fortified with extra folic acid, a synthetic form of vitamin B9, to reduce the number of babies born with spina bifida (babies born with the condition grow to adulthood with paralysis and bowel and bladder incontinence). The move was supported by the Food Standards Agency.

Folate is found in many foods, particularly green vegetables. Experts agree, however, that diet is unlikely to provide enough of this vitamin, so all mothers-to-be are currently urged to take folic acid supplements.

Compulsory fortification already happens in the US, Canada, Costa Rica, South Africa and Chile, and the number of neural tube defects, such as spina bifida, has been cut by between 19 and 55 per cent. In the UK, between 700-900 pregnancies each year are affected by neural tube defects – which could be avoided, some experts say, if folic acid were added to bread.

Ministers have not yet gone ahead with the proposal. However, following a further review of the evidence in 2017, the SACN continues to recommend mandatory folic acid fortification of flour, saying it would be the most effective way to increase folate intake in women in socioeconomically deprived areas.

Some consumers argue that compulsory fortification of all flour restricts their choice. But there are potential health issues, too, as some research suggests that the over-consumption of folic acid may increase the risk of certain cancers and, in elderly people, lead to brittle bones. There is a more complex story behind the cancer claims – whilst supplementation with folic acid seems to prevent cancer in its initial stages, it may also promote the disease in cells that are already cancerous. A 2018 study in bladder cancer patients suggested that patients who supplemented with high levels of folic acid were more likely to have their cancer recur within five years.

If a wonder pill existed that could prevent some of society's biggest killers, should all adults be taking it? Controversy flared in 2003, when two British doctors proposed the idea of a polypill – a mix of aspirin (to prevent blood clots), a statin (to lower cholesterol) and three agents to lower blood pressure, plus folic acid (based on limited evidence that it lowers certain amino acids linked to heart disease). They argued that, if taken daily by all people aged over 55, this polypill could slash heart attacks and strokes by more than 80 per cent.

Hold on, said critics – such a pill would medicalise life and undermine an individual's responsibility to keep fit. Dutch scientists came up with an alternative. Forget the pills, they said, and dine regularly on the 'polymeal': fish, garlic, almonds, fruits and vegetables, dark chocolate, and wine. These natural alternatives could cut heart diseases and would be more enjoyable, too.

In 2019, researchers reported that they had tested new 'polypills' in a study of over 50,000 Iranian people. The pills, containing aspirin, a statin and two blood pressure-lowering drugs, reduced serious cardiovascular events including heart attacks and strokes from 9 to 6 per cent. Whilst the researchers reported very few adverse effects, some experts argue against a 'one-size-fits-all' pill.

Sex differences in drug responses

Will we ever have 'his 'n' hers' medicines?

Until recently, men and women were assumed to be identical, pharmacologically speaking: if a drug worked on men, it should be fine for women. Male and female physiologies differ markedly, however, and recent studies have explored whether these differences could affect both the efficacy and side-effects of medications.

Among known or potential medical sex differences are:

- Women may suffer more severe reactions to some anti-HIV drugs – in some studies they were more likely than men to switch drugs due to side effects.
- Some lung cancer treatments may work better in women (although others may work less well).
- The drug alosetron is licensed for severe inflammatory bowel disease in women only. However, whilst some studies suggest only women benefit from the drug, others have shown that men benefit too.
- Certain painkillers seem to work better in women, though recent research suggests the differences may be more related to genetics than they are to gender.

Overall, we simply don't know enough about sex differences. This is partly because women were explicitly ruled out of drug trials in the 1970s, for fear that medications might harm an unborn child early in pregnancy. That situation is changing; in most cases women are now enrolled, but the data are not always analysed by sex to see whether sex differences exist.

One problem is that to break down a study group like this, greater numbers of participants are needed – increasing the cost and complexity of the trial.

Ethnic differences in responses

Drugs that could target disease in certain ethnic groups are causing controversy

Some diseases are known to affect certain human populations particularly severely. Sickle-cell disease, for example, mainly affects people of African, Caribbean, Asian, Middle Eastern and eastern Mediterranean descent. Diabetes is six times more common in people of South Asian origin than in the general population.

Although such observations are relatively uncontroversial, the idea that medicines could be targeted at particular ethnic groups is an ethical hot potato.

The difficulty is both scientific and social. For a condition such as sickle-cell disease, the cause of the high incidence is clear – it arises from a mutation in a haemoglobin gene, which has survived because it provides protection against malaria. But for more complicated conditions, the situation is less clear. Do biological or social factors underpin a high incidence of disease? Is heart disease in, say, someone from Denmark the same as that in someone from Bangladesh?

We currently don't know enough about disease mechanisms to answer such questions confidently. And the concern is that by proposing that genetic factors predispose certain groups to a disease, it may reinforce the idea of genetically distinguishable 'races' – something that touches upon a long and disturbing history of discrimination.

On the other hand, if factors specifically affecting one ethnic group could be identified, treatment for that group might be improved.

Of central importance is the notion of 'race'. Crucially, race is a social label, not a scientific one: it is one way in which society groups people, but it has no underlying scientific principles. Some people argue that it is useful – races may reflect some genetic substructure, including variation that affects health.

In 2005, BiDil became the first prescription drug to be approved for the treatment of congestive heart failure specifically in African-Americans. African-Americans have a high incidence of this condition, which involves the progressive weakening of the heart muscle, and do not respond well to other treatments. Its link to race has been further complicated by its economic backdrop. The drug was initially rejected by the US licensing authorities. After a reanalysis of clinical trial data, it was then 'reinvented' as a medicine for African-Americans, which provided new patent protection.

Although the clinical trial data suggested that African-Americans responded better to BiDil, many argued that this was not due to a genetic predisposition. It has been suggested that the difference in response was merely caused by the fact that the African-American patients were 'more ill' than people of the same age but different race.

The issue of race-based drugs remains a controversial topic. Race is a crude marker for variation in responses to drugs. It's possible that the rise of pharmacogenetics will enable a better understanding of how different groups of people have varying responses.

Individually tailored medicines

With advances in genomics, drugs could be individually tailored to our genes

One important justification for human genetic research is the prospect of medicines tailored to a patient's individual make-up – pharmacogenetics.

The idea is that a patient would be diagnosed with, say, heart disease and a doctor would do a quick test to find out which drug would work best on them and what does to use or which drug they shouldn't take because of its likely side-effects. It's an appealing vision, but how realistic is it?

There are some applications:

- Trastuzumab (Herceptin) is prescribed only for breast cancer patients with HER2 mutations.
- Imatinib is given to chronic myeloid leukaemia patients with a specific chromosome abnormality.
- The anti-HIV drug abacavir causes a potentially fatal reaction in 6 per cent of Caucasian patients and 2-3% of African American patients. Those with a specific gene variant are more likely to have the reaction. Screening for the gene variant is recommended before medication is given.

Among the most significant factors in pharmacogenetics are the cytochrome P450 (CYP) enzymes, which metabolise drugs and are found mainly in the liver. Many different forms of CYP enzymes exist, and each

form may have many variants – some make people poor metabolisers while others make them ‘ultrarapid’ metabolisers. The CYP2D6 enzyme, for example, plays an important role in metabolising about a quarter of all drugs and comes in over 100 different variants. CYP2D6 variations have been linked to responses to antidepressants as well as painkillers such as codeine.

Meanwhile, variations in another CYP enzyme predict how well people respond to warfarin - a drug that’s used to prevent blood clotting but can also cause excessive bleeding. People with a poor metaboliser variant of CYP2C9 are more likely to suffer excessive bleeding with warfarin, but there are now genetic tests available to health providers to determine who is at risk.

Whilst such examples show great promise, the translation of pharmacogenetics into clinical practice will not happen overnight. The identification of a variant linked to a particular drug response is only the beginning. Many factors are likely to influence the body’s response to a drug, and clinical trials will be needed to confirm that patients actually benefit from targeted treatment – something that so far has rarely been done. Even then, the practicalities of changing healthcare delivery will have to be tackled.

Industry will also have to respond to the pharmacogenetic challenge. Drugs being targeted to a subset of the population could mean that pharmaceutical companies are no longer able to produce ‘blockbuster’ drugs (drugs that are widely used and generate vast profits). Ruling out non-responders could dramatically reduce a drug’s market size.

On the other hand, a better understanding of disease will suggest new drug targets. Clinical trials could be streamlined – only responders would be included. Pharmacogenetics could identify groups at risk of an adverse reaction. This might mean a new life for drugs that work but are currently too risky to use.

Attitudes to drugs

We can’t seem to make up our mind about drugs

In 1979, author M N G Dukes described “the love–hate relationship which exists between the public and its drugs – substances which are hailed one moment as the solution to every problem and castigated the next as the cause of every ill”.

We’re consuming more medicines than ever before. We take for granted that they will cure our headaches, see off infections and lower our blood pressure. We give enthusiastically to medical research charities and see health-related research as a positive thing.

But we are terrible at taking medicines as instructed: around half of the people being treated for chronic conditions such as diabetes and high blood pressure do not stick to their prescriptions. We worry that we are overmedicating, giving young children a ‘chemical cosh’ (as Ritalin has been described) at the first sign of hyperactivity. Our final years are spent consuming a colourful cocktail of daily medications.

We have concerns about what drugs might do to us, and we don’t take them unless we absolutely have to. And yet we are happy to turn to ‘natural remedies’ that have been studied far less intensively, rarely have any track record of success and may contain a whole host of bioactive chemicals. Paradoxically, the word ‘clinical’ has come to mean something cold, logical and uncaring. How has it come to this?

The shift in attitude could be inflamed by a growing unease about conventional medicine. Pharmaceuticals-based medicine focuses on treating disease, not patients, in a highly mechanistic way. A quick consultation and here’s a prescription. Next.

By contrast, complementary therapies can seem caring and focused on the patient, not just the disease. Remedies may seem more ‘natural’ and kinder and be seen as a relatively safe way to improve one’s health, whatever the reality.