feature

Dr Colin Brewer

Fighting future

Block and parry

Long-acting antagonist drugs, which block the effects of heroin, cocaine, tranquillisers and even cannabis, may transform treatment within a few years

Recently Sri Lanka overtook Hungary as the country with the world's highest suicide rate (currently over 60/100,000 and rising – the UK is steady at about 12/100,000). This may not seem to have much to do with new developments in addiction treatment, but it does.

The main reason for Sri Lanka's high suicide rate is that the yellow oleander (*cerebra thevetia or thevetia nerifolia*[1]) plant grows everywhere. Its seeds have effects identical to those of digoxin – the active constituent of our common foxglove (*digitalis purpurea*).

Even a few oleander seeds can slow and eventually stop the heart, and practically everyone in Sri Lanka seems to know this. Because many of those who try to kill themselves are adolescent girls with boyfriend trouble, the deaths are more than usually tragic.

Since the late 1980s, it has been possible to treat deliberate or accidental overdose with a monoclonal antibody specifically designed to bind to and neutralise digoxin. In response to the epidemic of oleander suicides in Sri Lanka, physicians are now using this digoxin antibody and a recent study shows it to be highly effective.[2]

In Britain, the tricyclic group of antidepressants are commonly used in suicide attempts. They too are toxic to the heart but as with digoxin, a specific antibody for tricyclics can be made which blocks all their effects, including the toxic ones.[3]

As I pointed out over 10 years ago[4], if pharmacologists can synthesise chemicals that can block digoxin (or tricyclics), they should be able to synthesise substances that can block other drugs.

If these antibodies (technically antagonists) were given as part of a treatment programme, the large number of drug users and addicts who find it difficult to avoid relapse could use them to stay drug-free for long enough to have a chance to learn a new set of thinking and behavioural habits that don't involve the drugs in question.

About four years ago, reports started to appear of promising research with antagonists to cocaine and nicotine. There is also, apparently, an antagonist to cannabis.

There seems no reason why almost any drug should not be matched with a substance which blocks its effects directly, or increases its metabolism (so that taking the drug becomes uneconomic) or interacts to produce an unpleasant rather than a pleasant effect.

There are two types of antibody (or vaccine). *Passive* antibodies could block the effects of cocaine for a few months, like those holiday injections that give temporary immunity against hepatitis A.

Active immunisation involves

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vaccines that would make the body produce its own antibodies against cocaine (and presumably other drugs) as with immunisation against Hepatitis B, or tetanus. This could mean active immunity for many months or even years. It might even be possible to immunise children against the effects of nicotine at birth, as we now immunise them against measles.

We already have two effective antagonists – disulfiram for alcohol and naltrexone for opioids. Disulfiram (Antabuse) has been around for over 50 years and naltrexone for over 30.

Strictly speaking, disulfiram is a *deterrent* rather than an antagonist. It produces an unpleasant reaction in most people if alcohol is consumed, so it deters drinking in the same way that seeing a police car in your driving mirror deters speeding.

Naltrexone simply blocks opiate receptors so that even large doses of heroin, methadone or other opioids produce no opioid effects.

It is possible almost to guarantee that a patient who has been withdrawn from opiates can't relapse to opiate use for at least a month afterwards

With both drugs the problem is not that they don't work. They work so well that patients need a certain amount of arm-twisting to take them regularly. They work best when administered in ways which maximise compliance – taken as a condition of probation or under family supervision, for example.

Compliance solved

For the past three or four years, it has been possible to obtain crude but effective, implants of naltrexone, which seem to provide adequate blood levels for five to six weeks on average. They solve the problem of compliance and make supervision unnecessary.

This means that for the first time in the history of addiction treatment it is possible almost to guarantee that a patient who has been withdrawn from opiates can't relapse to opiate use for at least a month afterwards.[5] Since the first month after detox is when a high proportion of relapses occur, this is a useful development.

The first studies of long acting preparations of naltrexone date from the early 1970s. The results were promising but for a long time nobody took up the idea commercially.

Long-term blockade

Having fruitlessly pleaded with British pharmaceutical companies since the early '90s to turn their attention to a naltrexone implant, I am pleased that there is now a lot of interest in developing even longer acting naltrexone implants.

Trials are in progress with versions that may provide over six months of opiate blockade. Other opiate antagonists such as nalmefene, which is more potent than naltrexone and therefore could enable smaller implants to be made, are also attracting interest.

It is always dangerous to predict but if I am correct, the likely availability of a range of long-acting antagonists in the next few years will transform the treatment of people whose drug use – legal or otherwise – causes problems to them or to society. For where there can be no drug *effects* there can hardly be any drug-related *problems* for a particular individual.

When habitual drug users are deprived of their drug they usually function quite well eventually. It can take anything from a week to several months to recover completely from the withdrawal symptoms, depending on which drug is involved and individual susceptibility.

Until the late 1960s, drug users who went to prison had little chance of encountering drugs (including alcohol) while there. Almost invariably, they were eventually able to function as well as they had before they developed drug problems. Unfortunately, they nearly always resumed drug use when they left the artificial environment of the prison and returned to the real world with its temptations and memories.

Even today, many people leave prison drug-free but don't stay that way for long. The availability of effective, long-acting antagonists could change that.

The need for counselling would be greatly reduced. Just as the treatment of tuberculosis was enormously simplified once drugs were discovered that reliably killed tuberculosis bacteria, making special diets and open-air nursing obsolete, so will effective antagonists become the most important component of treatment, rather than the least important as they tend to be today.

Antagonists are powerful anti-craving agents. Their effect is not a direct pharmacological one on the alleged cerebral craving pathways but a simple psychological one based on their pharmacological properties.

Craving is a function of perceived availability. If a drug isn't actually available at its receptors in the brain, there isn't much point in craving for it in the sense of urgently debating whether or not to try to get some.

Civil liberty

Antagonists have implications for civil liberties as well as for addiction treatment. This is too big an issue to discuss here but I should make it clear that, like many citizens, I am opposed to the selective prohibition of recreational drugs. I believe we should return to something like Victorian values in these matters.

Until 1916, all mood-altering drugs were readily available to any adult citizen without causing the collapse of the Empire. In most respects, alcohol causes far more behavioural problems than all the illicit drugs combined.

One of the less publicised but occasionally terrifying aspects of the modern drug scene is the relationship between drugs such as amphetamine, cocaine, LSD and cannabis and severe mental illness. Apart from sometimes initiating psychotic behaviour, these drugs can seriously destabilise schizophrenics who might otherwise be safely treated in the community. Antagonists might prevent quite a few homicides and suicides in this group.

While there will still be a place for self-help and support groups, it will be a much smaller one. People who