

Artificial snow

As addiction experts undertake a trial to investigate whether an anti-tiredness drug can be used to treat cocaine dependency, **Tony D'Agostino** reports on the hunt for a methadone-style equivalent for stimulant abuse

Look closely at the opening scene of 2007 film *The Invasion*. Nicole Kidman plays a mother trying to save herself and her son from an alien virus that attacks when people sleep. Desperate to stay awake, she ransacks a pharmacy and grabs anything that will stop her nodding off – including a bottle of modafinil. And while the film is pure fiction, the drug and its ability to keep you awake and alert for long periods are fact.

Modafinil has been around since the early 1990s and is currently sold by the American pharmaceutical company Cephalon. As well as preventing sleep, it has also gained a reputation as a 'cognitive enhancer', thanks to its apparent ability to increase certain aspects of working memory such as performing calculations and pattern recognition.

It's a slow-acting drug – you'll need to wait a couple of hours or more before you feel its effects. But it has been reported that a 200mg tablet will make you feel alert and awake without the euphoria or subsequent comedown that accompanies the use of amphetamine or cocaine.

In the US, modafinil is used to treat sleep disorders, while in the UK the Ministry of Defence announced in 2006 that it was investigating the possibility of using the compound to keep military personnel awake. More recently, a pilot study currently being carried out by Professor John Strang and Dr John Marsden of the Institute of Psychiatry is looking at the possibility of using modafinil to treat cocaine dependency.

Not everybody who tries cocaine will become dependent, and many more people have tried the drug than have actually become dependent. But for a few individuals, quitting cocaine use is unimaginable, even when everything is telling them to stop. Cocaine predominately affects three chemicals in the brain, dopamine, serotonin and noradrenalin. These are the same chemicals released when we do things that give us a buzz – such as buying new clothes, funky gadgets or listening to good music – the same chemicals released when people gamble, eat food or play sport.

Because of the reinforcing effects of dopamine and also endorphins – in the long-term, cocaine hijacks these chemical pathways offering immediate gratification – individuals will go back again and again for that euphoric hit, to relive that moment, which they never quite reach again. Before 1968, physicians in the UK prescribed injectable cocaine to approximately 1,000 patients who were cocaine dependent. This is now virtually unheard of, and at present there are no randomised, placebo-controlled clinical trials exploring the efficacy of prescribing cocaine to cocaine-dependent users.

Using the same view and logic of methadone maintenance for the treatment of heroin dependency, a diverse set of chemicals have been proposed for the treatment of cocaine dependency. The closest studied stimulants so far are dexamphetamine and, more recently, modafinil.

To date, most pharmacological interventions have focused on relapse prevention. A multitude of drugs have been tested that work on dopamine receptors and calcium channel blockers, as well as anti-depressants, reuptake inhibitors, epileptic drugs and opioid blockers. The list is extensive. Yet no one chemical has proved to be truly effective.

A study in Cornwall tracked 60 stimulant users who were treated with dexamphetamine and found an equivalent reduction in illicit drug use and intravenous injection as those held on methadone. At the University of Pennsylvania in 2005 similar reductions in cocaine use were recorded, but this time the patients had been prescribed modafinil. It has been stated that modafinil has the opposite effects to cocaine in the withdrawal phase, and might therefore help people in the most difficult period of recovery.

Yet cocaine substitutes did not fair so well in a systematic review and meta-analysis carried out in Spain in 2007. The study looked at all randomized controlled clinical trials, comparing the efficacy of modafinil and dexamphetamine with placebos in cocaine dependent patients. Although the overall conclusion was that it could not be clinically proven that any of the stimulants improved retention or cocaine use, positive cocaine urine screens were lower for dexamphetamine, while secondary analysis also found promising results for modafinil.

So can modafinil offer new hope for those who want to get off cocaine? "It's an idea that really does need to be rigorously evaluated," says Frank Vocci, director of the pharmacotherapy division of the US government sponsored National Institute of Drug Abuse (NIDA). However, Dr Vocci also pointed out that the drug did not seem to work well with subjects who combined cocaine and alcohol.

In the Institute of Psychiatry pilot study, modafinil is being prescribed to 288 dual cocaine and opiate dependent clients, in conjunction with voucher-based reinforcement therapy for patients in methadone maintenance. Offering vouchers as an incentive to cut down cocaine use has proved successful in the US, and used in tandem with modafinil, it may enjoy similar results here. Yet both Dr Strang and Dr Marsden insist it is early days and that their feasibility study



Staying power: Modafinil was tested by the UK military because of its ability to keep people awake for days

is still in the set-up stage.

Some professionals are not optimistic about the benefits of modafinil. "Due to the complex multi-component pathways associated with drug reward mechanisms, and the powerful effects of stimulants such as methamphetamine or cocaine, a low threshold compound like modafinil will only have minimal effect in reducing cocaine craving," says Dr Richard Martin, pharmacologist and assistant head of services for Derby Drug Strategy Team.

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John Grabowski, a professor of psychiatry of the University of Minnesota, shares his skepticism, pointing out that modafinil has shown to be less effective on the most severely dependent cocaine users. "The more severely dependent people responded better to the more potent stimulants," he explains.

In its favour is the fact that modafinil does not seem to have the same dependency risk as amphetamine, making it a possible alternative as a maintenance drug. But again Dr Martin advises caution. "The same was said of other drugs – such as methadone – that are now deemed addictive," he says. "The trouble is, we don't know exactly how modafinil works on the brain."

The drug seems to affect the release of the sleep-promoting chemical GABA, along with glutamate – the most 'excitable' neurotransmitter. It also may stimulate the histamine system, which upsets sleep regulation because it increases alertness. Recreational use of modafinil in the UK is limited, with the

few posts present on underground websites merely confirming that there is no 'buzz' associated with the drug and that it simply keeps you awake.

The alternative to developing drugs that will treat cocaine dependency is vaccination. Currently being trialled, TA-CD introduces cocaine antibodies into the body so if you take cocaine you feel nothing: in effect, the cocaine doesn't 'work'. The main advantage of a vaccine is that it can be used in any cultural setting and on any age group with exactly the same effect. And TA-CD is showing very promising results.

Some eyebrows have already been raised, however. "Too many people are looking for the magic cure when we should be investing in drug workers' knowledge and competencies," says Aidan Gray, director of services for Rugby House. "For example, we just used specific cognitive behavioural group work and were scoring 55-60 per cent in getting users off crack and cocaine."

Aidan was instrumental in developing the first crack cocaine day programmes in the UK. "Take an inner-city crack user out of their environment and put them into a country house hotel, away from all possibility of scoring and you will see craving drastically reduced." Although the matter of the user returning home to their original environment has to be addressed.

Future treatment for cocaine dependence will undoubtedly incorporate many of the interventions discussed – there is preliminary evidence that when modafinil is combined with other psychosocial treatments it may improve clinical outcome. At present, anti-depressants, particularly selective serotonin reuptake inhibitors (SSRIs), are still commonly prescribed to treat cocaine use, despite the lack of evidence in their favour. If we are to follow where the evidence is taking us, however, an integrated approach between psychosocial and pharmacological interventions looks like the most likely candidate for success.

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