



# postnote

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## TREATMENTS FOR HEROIN AND COCAINE DEPENDENCY

Some 11.3 million people in Britain have used an illicit drug at least once in their lifetime.<sup>4</sup> Cocaine and heroin are the most damaging illicit drugs in terms of health impacts to dependent individuals and the cost of drug related crime. This POSTnote looks at the treatments currently available for heroin and cocaine dependency, assesses the prospects for new treatments, and examines the issues these raise.

### Background

This note focuses on two drug dependencies:

- Heroin, which is an opioid derived from a particular species of poppy plant. Other opioids include the pain relievers morphine, and codeine.
- Cocaine, which is extracted from coca leaves. It refers both to cocaine powder, which is water soluble and is 'snorted' or injected, and to 'crack' cocaine which is not soluble in water and is usually smoked.

Advances in the understanding of how drugs act on the brain are described in Box 1. These have led to the development of medicines to treat drug users. Such medicines are delivered in conjunction with psychosocial support and behavioural intervention (Box 2).

Untreated drug use creates significant costs to individuals, families and communities. These include property crime, violence, and expenses incurred by the criminal justice and healthcare systems as well as those to social services. The government estimates that class A drug use generates £15.4 billion in crime and health costs each year.<sup>1</sup> Recent data suggest that 161,000 people are receiving help for drug dependency through community drug treatment and a further 60,000 through the criminal justice system.<sup>2</sup> In England, two thirds of adults in treatment are primarily dependent on heroin, 6% on cocaine powder and 6% on crack. There is an emerging trend of poly-drug use (opiates and crack).

### Box 1 The Brain and Drugs

Different regions of the brain affected by drug use include:

- the brain stem, which controls critical functions such as breathing, heart rate and sleeping;
- the limbic system which contains the brain's 'reward circuit' (see below) and links together brain structures that control the ability to feel pleasure.

Nerve cells in the brain communicate with each other by releasing chemical 'messengers' (neurotransmitters) which travel across the gaps between the cells. A neurotransmitter released by one nerve cell travels across the gap to the next, and attaches itself onto a specific receptor on the outer surface of that cell. This triggers the second nerve cell to release an impulse, thus passing on the message. The neurotransmitter is then mopped-up and recycled, shutting off the signal between the nerve cells.

The brain is wired to ensure that life sustaining activities are repeated by associating those activities with pleasure or reward. Whenever its 'reward circuit' is activated, the brain encourages repeat behaviour. The reward circuit is activated by a neurotransmitter called dopamine. Dopamine is present in regions of the brain governing movement, emotion, cognition, motivation and feelings of pleasure. Heroin and cocaine over-stimulate the reward system by flooding it with dopamine, producing the euphoric effects sought by drug users. Dependence on these drugs can then be 'learnt' in the same way that the body learns life sustaining activities.

### Current Government Drugs Policy

The Government's ten-year drug strategy (2008-2018) has four themes: protecting communities; preventing harm to children, young people and families; delivering new drug treatments; and public information and engagement. The strategy aims to expand and improve drug treatment services by:

- tailoring drug treatment to individual needs;
- achieving higher completion rates for people on treatment programmes;
- increasing understanding of addiction and identifying new forms of treatment and prevention.

### Box 2. Psychosocial Interventions

These are broad approaches to help the patient to stop and/or abstain from using drugs. Guidance on psychosocial interventions for drug misuse recommends the following:<sup>3</sup>

- Brief interventions – opportunistic interventions focused on motivating people with limited contact with drug services. These should provide non-judgmental feedback and explore ambivalence to drug misuse.
- Behavioural couples therapy - for people who are in close contact with a non-drug-misusing partner. The intervention should consist of at least 12 weekly sessions and focus on the service user's drug misuse.
- Family therapy – this recognises that a person's drug dependency can affect a whole family. Where appropriate, a therapist can help the family to communicate more effectively while the patient reduces his or her drug use.
- Contingency management – use of incentives to reinforce positive behavioural change and promote patient engagement with drug services.
- Mutual support – providing information about self help groups such as Narcotics Anonymous and Cocaine Anonymous.
- Cognitive Behavioural Therapy - patients working with a therapist to look at how their problems, thoughts, feelings and behaviour fit together. NICE recommends such treatment for depression and anxiety disorders in people undergoing drug treatment.

In addition, the National Treatment Agency recommends mapping, a technique that involves drug workers visually representing their client's thinking in a series of maps to improve their engagement and motivation.

The main difference between treating heroin and cocaine dependency is that there is no effective substitution prescribing for cocaine. Current treatments recommended by the National Institute of Health and Clinical Excellence (NICE) for heroin dependency include medication such as methadone or buprenorphine and psychosocial interventions (Box 2). For cocaine dependency, treatment is based primarily on psychosocial interventions and support from key workers.

### Heroin

Heroin acts on the opioid receptors that are usually activated by 'natural opioids' (endorphins). When heroin or endorphins bind to the opioid receptors, the brain's reward system (Box 1) is indirectly stimulated. Heroin penetrates the brain more rapidly than other opioids, which is why many addicts prefer it. It causes a brief intense euphoria, followed by a few hours of a relaxed, contented state. Excessive release of dopamine and stimulation of the reward circuit can lead to repeated use (Box 1). Frequent heroin use can lead to addiction and increased tolerance of the drug, so that larger doses are needed to obtain the same effect. Heroin also acts directly on the brainstem (Box 1) resulting in a decreased breathing rate. Heroin overdose can cause the respiratory centre to shut down breathing altogether, leading to death. Over-doses tend to occur when heroin is mixed with other sedative drugs or when taken after a period abstinence (when tolerance is reduced or lost).

Withdrawal symptoms are one of the main reasons why people continue to take heroin and why relapse is common in patients trying to overcome heroin use.

### Box 3. Methadone Treatment

Methadone acts as a substitute for heroin because it mimics some of its pleasurable actions. It is metabolised more slowly than heroin and exerts its effects over a longer time period. This means that methadone has a reduced rate of onset, and when taken orally gives a more muted 'rush' compared with heroin. A patient taking a single oral dose of methadone will be relatively free from cravings for the whole day. This helps to stabilise a patient's life compared with a heroin addict, who needs more frequent (2-4 per day) heroin hits. Provided it is prescribed at an appropriate dose, once methadone has been taken, the desire to use heroin will be reduced or even abolished. Methadone is a very addictive drug in its own right. It can be fatal in overdose and can be diverted for illegal street use. In such use, toxicity is enhanced when the drug is taken with diazepam tranquilisers and alcohol because each of these is metabolised by the same enzyme.

Symptoms typically begin 6 to 8 hours after the last dose of heroin, with the most severe occurring within 48 to 72 hours and lasting for about a week. These can include anxiety and drug cravings, dilated pupils, loss of appetite, shakes, muscle cramps and depression.

### Current Treatments for Heroin Dependency

In 2007/08, 61% of patients in drug treatment had heroin as their primary drug of misuse.<sup>4</sup> Currently, in the UK, the main approach to the pharmacological treatment of heroin addiction is the use of substitute medication. The most widely used substitute is methadone (Box 3) but others are available such as buprenorphine.<sup>5</sup>

#### *Methadone*

Methadone has been proven to be an effective treatment for heroin dependence. It helps patients to stabilise their lives and allows them time to consider moving towards abstinence. NICE recommended methadone treatment for heroin dependency in 2007.<sup>5</sup> The Advisory Council on the Misuse of Drugs (ACMD) review of the use of methadone treatments identified four main benefits:<sup>6</sup>

- decreasing illicit drug use (heroin);
- decreasing the number of people injecting drugs, thereby reducing the risk of transmission of viruses;
- reducing the risk of death from opioid overdose;
- decreasing the level of criminal activity.

Methadone treatment will be effective only when accompanied by appropriate psychosocial interventions (Box 2). A decision to start a patient on methadone is based on a detailed risk assessment, and the role of prescribers and others involved in delivering drug treatments is laid down in guidance from the National Treatment Agency (NTA) and the Royal College of Psychiatrists.<sup>7</sup> Guidance from NICE and the Department of Health in 2007, reiterated existing advice that new patients being prescribed methadone should be required to take their daily doses under supervision for a period of three months. This presents regular opportunities for health promotion and allows for daily monitoring with feedback to the patient's key worker or prescriber.

An ACMD review has noted that methadone has a "fairly narrow window of safety"; the difference between the dose needed for maintenance and the dose that can kill is small. The review raised concerns about the gap

between prescribing practice and clinical guidelines. Since then, the NTA and Healthcare Commission have reviewed whether prescribing was in line with clinical guidelines, and each local drug service has reviewed its practice to see if it is compatible with the guidance. The number of deaths related to methadone use in England and Wales rose, from 201 to 325, between 2003-07.<sup>8</sup> Further research is needed to assess the possible reasons for this, but one factor may be the rise in the number of people receiving drug treatment in the community.

#### *Buprenorphine*

Buprenorphine was licensed for use in opioid dependency in the UK in 1999. It binds tightly to the opioid receptors and thus reduces the impact of additional opioid use. Some patients respond better to methadone and others to buprenorphine treatment. Buprenorphine produces a milder, less euphoric and less sedating effect than equivalent doses of methadone, but still prevents or alleviates opioid withdrawal including craving.

#### *Naltrexone*

Naltrexone is a treatment that works by blocking the opioid receptors in the brain. It is neither reinforcing nor addicting and has no potential for abuse. However, the absence of rewarding effects means that patient non-compliance is a problem. Naltrexone is thus most useful for highly motivated patients. It can be taken once daily or every other day, but before the first dose the patient must have been opioid-free for 7-10 days. If there are opioids in the patient's system, naltrexone will very quickly displace them from the receptors, and send the patient into instant withdrawal. Because naltrexone binds to opioid receptors very tightly, it blocks the euphoric effects of opioids as well as the reinforcement effects, thus gradually reducing the desire to take opioid drugs.

### **Developments in Treatments for Heroin Dependency**

#### *New Methadone Formulation*

Current methadone treatments are made up of a mixture of two forms, which have a different 3-D shape (each is a mirror image of the other). Only one of these forms, levo-methadone, is active at the opioid receptors in the brain. A German company developed a process for separating the two forms but the pure methadone proved to be too expensive. More recently, scientists in Manchester have developed an enzyme-based process for making pure batches of either form of methadone using cheap starting materials. The patent is now held by Intellprogranix Ltd, which is keen to test the different forms in Phase I and Phase II clinical trials. There is some interest in testing levo-methadone as a treatment for heroin dependency, while the other form (dextro-methadone) has potential value in treating some types of pain.

#### *New Delivery Mechanisms*

Newer formulations of buprenorphine are being developed to enhance the long-term delivery of treatment. In 2008, a US company tested an implant designed to deliver six months of continuous therapeutic levels of buprenorphine. In a small trial of 163 patients addicted to opioids, a statistically significant higher proportion of the patients receiving buprenorphine were drug free after 16 weeks, and the implant was reported

to be well-tolerated and safe. Long-term naltrexone implants are also being investigated. For instance, a study is under way in Russia investigating an implant that blocks opioid receptors for 8 to 10 weeks.

#### *Treatments for Withdrawal*

In users who suddenly stop taking opioids, the natural balance between endorphins and another neurotransmitter, noradrenalin, is disturbed, resulting in withdrawal symptoms. Methadone treatment alleviates such symptoms. The drug lofexidine holds back the release of noradrenaline, helping to reduce withdrawal symptoms. It does not activate the reward circuit or stop the craving for opioids, but merely helps to alleviate the physical symptoms. NICE recommends that lofexidine be considered for people who have decided not to use methadone or buprenorphine for detoxification, those who want to detoxify within a short time period, and those with mild or uncertain dependence.

### **Cocaine**

Cocaine stimulates the central nervous system, directly hijacking the reward centres in the brain (Box 1). It does this by binding to receptors on the nerve cells in the brain that are normally responsible for removing dopamine from the system. The resulting build up of dopamine leads to over-stimulation of the reward pathway. This in turn produces extended and amplified sensations of pleasure to create a forced euphoria - an artificial 'high' associated with cocaine use. This is followed by a 'crash' or 'comedown' that can result in the immediate and overwhelming desire to take more.<sup>9</sup>

Cocaine can cause a wide range of effects including increases in heart rate and blood pressure, anxiety, panic, paranoia, confusion, dilated pupils, hallucinations, tremors and hyperactivity. Cocaine withdrawal symptoms include anxiety, depression, fatigue, sleep disturbances, appetite changes and irritability. When injected, the effects of cocaine wear off within an hour. As a result cocaine injectors often increase the frequency of injecting which can cause physical damage, and in rare cases, overdose. A cocaine overdose can cause heart attack or seizures, brain haemorrhage due to increased blood pressure, a dangerous rise in body temperature, kidney failure, delirium, convulsions and death.

### **Current Treatments For Cocaine Dependency**

Current clinical guidelines in the UK do not recommend any substitute prescribing for cocaine. Psychosocial interventions (Box 2) are the mainstay of treatment. For instance someone who primarily uses cocaine powder but has a short history of use may benefit from a brief motivational intervention (Box2). In contrast, someone who uses crack cocaine in conjunction with opioids may benefit from contact with key workers and contingency management (Box 2). Various treatments are in development including substitutes and vaccines.

#### *Cocaine Substitutes*

A number of potential substitutes for treating cocaine dependence are in development. The National Institute of Drug Abuse in the US rapidly screens existing medications and conducts clinical trials on those that could be effective. It has five promising medications in

phase II clinical trials, one of which (DAS431) is a substitute that directly binds to the dopamine receptors in the brain.<sup>10</sup>

#### Treatments for Cocaine Dependence

Disulfiram (Antabuse) is a drug used to treat alcohol dependency. However, when it is given to patients who are addicted both to alcohol and cocaine, disulfiram reduces cocaine use as well as alcohol use. Research is thus under way to investigate whether disulfiram might be an effective treatment for cocaine dependency. Studies in the US have shown that disulfiram-treated patients had a sustained physiological response to cocaine and reported that they experienced unpleasant, often anxiety-related, effects from it.<sup>11</sup>

#### Vaccines

Another strategy to treat cocaine dependency is by immunisation with a vaccine (Box 4). Cocaine and other drugs are too small to elicit a response from the body's immune system. However, by attaching cocaine to larger molecules, researchers have been able to develop vaccines that are recognised by the immune system, which releases antibodies in response to them. The hope is that these antibodies will also recognise and bind to any (normal-sized) cocaine molecules they encounter in the blood. This would effectively remove cocaine from the system, because the resulting antibody-cocaine complex is too big to pass into the brain.

#### Box 4. The TA-CD Vaccine

Celtic Pharma has developed a cocaine vaccine (the TA-CD vaccine) and conducted small scale clinical trials using it to treat addicts with cocaine dependency. The vaccine has to be given frequently (studies to date have been based on a vaccination schedule of every two weeks for a period of up to 8 weeks) to build up sufficient levels of antibodies against cocaine in the blood. Early clinical trials established that the vaccine was safe and well tolerated. Patients proved difficult to monitor, but some effects were seen. Celtic Pharma believes that the vaccine has the potential to reduce dependence and use or even to stop cocaine use completely when used in conjunction with counselling therapy. The company is currently focused on optimising the dosing regimen with further (phase II) clinical trials planned for late 2009/early 2010 in Spain, Italy and the US, and considers it unlikely that the vaccine will be available before 2014.

## Ethics of Drug Treatment

### Vaccines

Vaccination against cocaine would have potential benefits, but also raises ethical issues. For instance, it has been suggested that use of such a vaccine could be mandated by the criminal justice system, perhaps as part of a sentence for offenders with a known cocaine problem. However, mandatory use of a vaccine would be controversial as it raises questions of human rights, and could deprive people of choices about their lifestyle. Using a vaccine therapeutically, to wean people off cocaine use, is less ethically contentious provided that informed consent can be obtained. Extra help may also be needed to combat the behavioural aspects of addiction, by addressing: the ritual aspect of drug use; the environment it takes place in; and the company that cocaine users keep.

### Targeting High Risk Groups

In recent years, researchers have identified factors that may be linked to an increased risk of drug dependency. For instance, certain genetic sequences appear to be more prevalent in people with drug dependency. There is also some suggestion that brain imaging may be used to detect differences between addicts, potential addicts and non addicts. One possible consequence of this type of research is that groups identified as being at highest risk could be more carefully monitored and offered counselling. However, the evidence linking such factors to increased risk of addiction is far from conclusive.

### Clinical Trials

Considerable investment is needed if the new medicines to treat drug dependency are to be developed. One problem here is that big pharmaceutical companies have been reluctant to associate themselves with this field. However, with evidence that such treatments can bring financial rewards (medicines to treat nicotine dependence) such positions are beginning to change. Another major issue with clinical trials for such treatments is lack of patient compliance. This may be due to the lifestyle of drug users not being conducive to keeping the regular appointments needed to administer treatment and monitor its effects.

### Overview

- The government's ten-year drug strategy (2008-2018) aims to increase understanding of addiction and continue to improve drug treatment and prevention.
- New formulations of existing medications, new substitutes and new treatments to manage withdrawal are all being developed for heroin addiction.
- Preliminary studies on new vaccines are promising for the treatment of cocaine addiction. However, there are issues regarding the ethical aspects of their use.
- Investment is needed to bring treatments with positive preclinical evidence into testing in clinical trials.

### Endnotes

- 1 *Drugs: Protecting families and communities*, HO 2008
- 2 NTA, *Story of drug treatment*, 2009
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