European Monitoring Centre
for Drugs and Drug Addiction

PERSPECTIVES ON DRUGS

Treatment for cocaine dependence: reviewing current evidence

While cocaine remains the most commonly used illicit stimulant in Europe, challenges still exist around the provision of treatment to users. Regular cocaine use has been associated with cardiovascular, neurological and mental health problems, as well as with increased risk of accident and dependence. Currently, psychosocial interventions are the primary treatment options for cocaine dependence, with studies showing contingency management as effective. At the same time, several trials are investigating various pharmacological treatments for cocaine dependence. This summary analyses a set of systematic reviews of medications for cocaine users and looks at their role in reducing use and cravings, and their acceptance by users.

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pods/treatments-for-cocaine-
dependence

Problem cocaine use and treatment in Europe

Despite declining or stable levels of cocaine use in most countries, an estimated 2.2 million young adults (aged 15–34) used the drug in the last year. While many cocaine users will not experience problems related to consumption, a small but significant minority will be in contact with drug services because of health-related problems linked to the drug itself and the route of administration. These can range from problems with dependence, to cardiovascular and mental health issues, to blood borne viral infections such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV) (EMCDDA, 2014). In the European Union 55 000 (14 %) of all reported clients entering specialised drug treatment in 2012 reported cocaine as their primary drug. Given the prevalence of cocaine use, the number entering treatment and the different types of cocaine users finding effective treatments is an ongoing priority.

Types of pharmacological treatments

Pharmacological treatment options available for clients with heroin problems have been available in drug treatment services in much of Europe for a number of decades, most commonly provided in the form of methadone and buprenorphine. However, such a medical solution has so far been elusive for treating clients with problems linked with the use of illicit stimulants, such as cocaine and amphetamines. Nevertheless, a number of medications have been examined

to explore whether they may play a role in the spectrum of treatment options being offered for cocaine problems. These medications have been registered for a range of other medical conditions (see figure) and were not origina proposed for the treatment of cocaine users. As such, the drugs are being used in an 'off-label' (not indicated) way i trials. In general, these medications are used to treat coca users in conjunction with various psychosocial interventic such as contingency management (see 'Psychosocial interventions for treating cocaine problems').

Psychiatric and anticonvulsant medications, and several classes of drugs that modulate the brain's dopamine system, have been examined to establish whether they can be used to treat cocaine problems. These drugs can help to regulate the systems in the human brain that carry neurotransmitters, which are naturally occurring chemicals within the brain used to control and regulate psychological and physical functions (see video online). Cocaine blocks the uptake of a neurotransmitter called dopamine. As this depletes the level of dopamine available in the brain, medications that can halt this process and alleviate its side effects are considered the most promising in the treatment of cocaine users.

Two types of psychiatric medications, antidepressants and antipsychotics, have been studied in the treatment of cocaine users. Antidepressants are normally used to treat people suffering from depressive disorders. Cocaine use can lead to depression because it affects the monoamine system (involved in mood regulation). For this reason antidepressants have been tested among cocaine users to see if they can reduce short-term post-cocaine depression and craving. Antipsychotic medications are used to treat mental disorders, such as schizophrenia and bipolar disorders (in particular, manic episodes). Studies have been undertaken to evaluate their role in treating cocaine users experiencing hallucinations, delusions and other psychotic symptoms.

Use of cocaine may enhance dopamine transmission and deplete dopamine concentrations in the brain. As a result, dopamine agonists could, theoretically, reduce these symptoms in cocaine users. Central nervous system stimulants are used to treat conditions such as attention deficit hyperactivity disorder (ADHD). In particular, these stimulants indirectly increase dopamine and, if administered orally along with long-lasting compounds, can counteract the depletion of dopamine that arises from cocaine addiction. As a result, a number of these stimulants have been tested to see if they can work as substitution treatments for cocaine users.

Medications from several different classes of drugs have been identified as potential treatments for cocaine users as a result of their ability to block the release of the neurotransmitter dopamine within the brain. This includes anticonvulsants,

Groups of mediactions tested

Psychostimulants	Anticonvulsants	Antidepressants
Selegiline	Carbamazepine	Bupropion
Modafinil	Gabapentin	Desipramine
Methylphenidate	Phenytoin	Imipramine
Mazindol	Tiagabine	Nefazodone
Dexamphetamine	Topiramate	Ritanserin

Dopamine agonist	Disulfiram	Antipsychotic
Pergolide		Olanzapine
L-dopa/Carbidopa		
Bromocriptine		
Amantadine		

Disulfiram, and opioid receptor antagonists. Anticonvulsant (or antiepileptic) medications are used to treat seizures in people with epilepsy. As these drugs are supposed to balance the dopamine system and effectively block the addiction-related effects of cocaine, some studies have examined their use in treating cocaine users. Disulfiram is one of several medications that have been used to treat alcoholism. It inhibits an enzyme involved in the metabolism of alcohol, making the experience of drinking very unpleasant, which is intended to discourage its consumption. Recent studies have indicated that Disulfiram can be used to treat cocaine addiction as its mechanism of action results in a modulation of dopamine in users' brains. Naltrexone has been used in the treatment of alcoholism and, to a lesser extent, in the management of opioid dependence. It is an opioid receptor antagonist and can reduce cocaine craving and relapse rates among dependent users.

What can research tell us?

As highlighted above, a number of medications have been trialled, but is there any evidence of their effectiveness in treating cocaine dependence and related problems? In order to try to answer this question, six systematic reviews of the research examining the use of medications for treating cocaine dependency have been undertaken by the Cochrane Group on Drugs and Alcohol (www.cochrane.org; cdag. cochrane.org/our-reviews). These reviews attempt to make sense of the results of all the individual studies for each class of drug published between 1985 and 2010. This covered 92 individual studies, 85 of which were conducted in the United States, and included a total of 7 363 participants. This summary presents a meta-analysis of the original reviews, in order to clarify the role played by the drugs and to identify which are most effective (Amato et al., 2007; Minozzi et al., 2008; Castells et al., 2010; Pani et al., 2010; Amato et al., 2011; Pani et al., 2011). Three statistical techniques have been used to assess the reviews and examine the main results for patients. Multiple-treatment meta-analysis (MTM) allowed comparison of interventions across studies; surface under the cumulative ranking curve analysis (SUCRA)
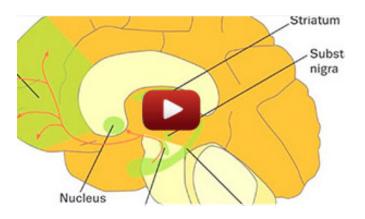
involved ranking the competing treatments according to the study outcome; while pair-wise meta-analysis was used to compare the experimental interventions against controls. These statistical methods were used to explore whether different medications were associated with three outcomes: reducing the use of cocaine, reducing cocaine-related craving and retention of cocaine users in the treatment programme.

These statistical techniques produced mixed results for the efficacy of medications in reducing cocaine use, as shown in the table.

Overall, antipsychotic medications appeared the most effective at reducing users' cravings for cocaine. Here, MTM showed statistically significant results that antipsychotic and antidepressant drugs were effective when compared with placebo. Similarly, in the analysis of the ranking (SUCRA) with all the other medications, the antipsychotic drugs scored highest (97 %) at reducing craving. The pair-wise meta-analysis also showed that the antipsychotic drugs had a limited, but statistically significant, advantage over placebo and over anticonvulsants

Patient drop-out levels, or the number of patients leaving the studies before their conclusion, were used as a measure of acceptability of interventions to cocaine users. A mixed set of results was generated by the MTM analysis for this issue. Disulfiram was better than placebo, versus anticonvulsants, and versus antidepressants, at retaining users in treatment. Patients given opioid antagonists remained in treatment for longer periods than those given anticonvulsants. A similar picture emerged from the SUCRA ranking analysis, where Disulfiram and opioid antagonists were also shown to be better accepted treatments by users. Of these two medications, Disulfiram, showed more favourable results when the pair-wise meta-analysis of three studies comparing opioid antagonists versus Disulfiram was undertaken.

| Interactive element: video

Video on treatment for cocaine dependence, available on the EMCDDA website:
emcdda.europa.eu/topics/pods/treatments-for-cocaine-dependence

Statistical techniques used

Analysis	Description	Narrative results
MTM	Comparison of interventions across different studies	None of the studied drugs significantly reduced the use of cocaine when they were compared to all the other medications and to placebo
SUCRA	Hierarchy of the competing treatments	Dopamine agonists and antipsychotic medications had the highest levels of efficacy for reducing cocaine use
Pair-wise meta-analysis	Comparison of studies	None of the pharmacological interventions were shown to be better than placebo in reducing the use of cocaine

| Conclusions

To date, a range of different medications have been trialled to assess their use in the treatment of cocaine users. This has largely revolved around testing the use of medications established as treatments for other conditions. A mixed picture emerges from the systematic reviews of research evidence conducted to date regarding what might best be used to treat cocaine users. This new analysis of existing reviews suggests that antipsychotic medications appear to be the most successful at assisting users to cease use and overcome cravings for use, while Disulfiram is the most accepted treatment by users. Nonetheless, none of these medications has yet been established as effective treatment in the same rigorous way as, for example, methadone has been for opioid dependence. Several classes of drugs remain under ongoing analysis to provide treatment for users, and work is continuing on preventative and cessation measures, such as the use of a cocaine vaccine (EMCDDA, 2010). What remains clear in the challenge of constructing a set of interventions for cocaine users is that psychosocial interventions have a proven effectiveness. When coupled with a suitable medication, these interventions, such as contingency management, may form the core components of an effective treatment intervention for cocaine users.

Psychosocial interventions for treating cocaine problems

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In the absence of an established pharmacotherapy for cocaine dependency, treatment options have made use of psychosocial interventions. While including a range of different measures, these interventions can be regarded as being structured therapeutic processes addressing both psychological and social aspects of a user's behaviour, varying in terms of their duration and intensity (Welsh Government, 2011). Three general types of psychosocial intervention have been used to treat drug users: cognitive behavioural therapy, motivational interviewing and contingency management. In practice there are many subtypes, variations and overlaps in the specific measures offered by service providers in different countries.

Cognitive behavioural therapy (CBT) is a psychotherapeutic treatment modality that can be offered in an individual or group format (Hofmann et al., 2013). It is empirically supported as a treatment for substance use disorders. In general, CBT interventions involve challenging irrational, negative thinking styles that are thought to promote negative affective states, which in turn promote maladaptive behaviours. CBT interventions promote the development of alternative coping skills and focus on changing behaviours and cognitions related to substance use through self-control training (e.g. stimulus control techniques), social and coping skills training and relapse prevention. Initial treatment sessions often involve developing skills directly related to achieving and maintaining abstinence (e.g. drug use self-monitoring, refusal and craving coping skills, increasing social support and non-drug-related activities, problem-solving training, coping with relapse). Later CBT sessions may focus on topics and skills indirectly related to maintaining abstinence (e.g. anger/frustration and anxiety/depression management, impulse control, self-efficacy, effective communication).

Motivational interviewing (MI) is a client-centred, semi-directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence (Smedslund et al., 2011). It seeks to harness an individual's motivation to engage with the treatment process. As a result, it is often used at the outset of treatment to help motivate clients to try more intensive measures, such as CBT. MI has been shown to be effective with both adults and adolescents and is an empirically supported intervention for substance use disorders. It is especially useful when clients are ambivalent about changing their behaviour. In providing MI-based interventions, therapists ask open-ended questions, provide affirmations to the client, listen reflectively and summarise the client's statements (Schettino et al, 2014).

Contingency management (CM) is a type of treatment used in the mental health or substance use fields. Clients' behaviours are rewarded (or, less often, punished) in line with treatment objectives and adherence to, or failure to adhere to, programme rules and regulations or their treatment plan (Griffith et al., 2000). Clients can be, for example, rewarded with vouchers that can be exchanged for retail items (Vocci and Montoya, 2009).

Several reviews have been undertaken to examine the effectiveness of psychosocial interventions for treating drug problems. For example, a systematic review (Knapp et al., 2007) showed that CBT interventions reduced drop-out from treatment and use of cocaine; this was especially true when accompanied by a contingency management approach. In particular, CM interventions have been shown to help to improve retention in treatment and, in turn, other treatment outcomes (Vocci and Montoya, 2009). Consequently, measures following this approach to treating cocaine dependency rank as the psychosocial intervention with the highest efficacy (Vocci and Montoya, 2009). More recently, a Belgian study reported that after six months of participation in a CM programme with community reinforcement, the rate of abstinence among cocaine users was three times higher than for clients in standard treatment (Vanderplasschen et al., 2011).

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| Key definitions

The evidence in support of interventions is based on individual studies and systematic reviews of evidence. Generally, studies compare an experimental intervention against a placebo or a control intervention, rather than against other competing interventions. Consequently, these comparisons are of limited use in informing clinical decision-making, which is better served by the results of so-called 'head to head' comparisons. These trials compare two medications against each other, highlighting their strengths and weaknesses, so the one most suited to 'real world' everyday use can be identified. Meta-analytic techniques allow us to overcome some of the problems arising from indirect comparisons and extract useful results from various existing studies. The three meta-analytic techniques used in this summary are defined below.

Multiple-treatment meta-analysis allows comparison of interventions across different studies (Caldwell et al., 2005). It allows us to overcome some of the problems arising from indirect comparisons by generating results that remain consistent across the protocols and inclusion/exclusion criteria for patients' enrolment across different studies..

Surface under the cumulative ranking curve analysis (SUCRA)

SUCRA analysis is used to provide a hierarchy of the competing treatments. The larger the SUCRA value, the better the rank of the treatment (Chaimani et al., 2013).

Pair-wise meta-analysis of studies is, in contrast to the other two approaches, a method based on direct comparison. It involves a pooled analysis of studies comparing an experimental intervention against a control.