



European Monitoring Centre
for Drugs and Drug Addiction

Treatment of problem cocaine use – a short update

Summary

A number of agents with different actions on the dopaminergic system have shown positive preliminary results. However, due to the limited number of trials, it is difficult to determine which one yields the most promising therapeutic outlook. Some appear to stand out (e.g. modafinil, disulfiram or the cocaine vaccine), although larger clinical trials are necessary to assess the effectiveness of these potential treatments.

Finally, pharmacotherapy is unlikely to provide a 'magic bullet' and a general lesson from the experience of treating other types of drug problem is that they are likely to be most effective if accompanied by appropriate psychosocial interventions and support.



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Treatment of problem cocaine use – a short update

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Introduction

There is an overall consensus in the literature that the treatment of cocaine and crack cocaine dependence is associated with high attrition and relapse rates (Dutra et al., 2008). Unlike opiate treatment, no approved pharmacological treatment options are currently available to help cocaine dependent users maintain abstinence, reduce use or diminish the strong cravings experienced during this period. However, a number of prescription medications have shown potential to reduce cocaine consumption and cravings in clinical trials.

The choice of testing particular (candidate) pharmaceutical agents in pre-clinical and clinical trials is largely based on the dopamine (DA) hypothesis of cocaine's action (Dackis and O'Brien, 2001). Through its DA reuptake inhibitory mechanism, cocaine elevates dopamine transmission in the reward system of the brain which is thought to be a primary mediator of addiction to cocaine. Essentially, molecules are considered potential therapeutic agents when they either increase dopamine release, thus reducing cocaine withdrawal symptoms and craving, or inhibit dopaminergic activity, thus reducing cocaine's reinforcing effects.

Pharmacotherapies

Used in the treatment for alcohol dependence, disulfiram acts on the enzyme dopamine beta hydroxylase and blocks dopamine conversion into norepinephrine which increases dopamine levels in the brain.

Disulfiram has shown in six randomised clinical trials to reduce the number of cocaine-positive urines in cocaine-dependent users. Furthermore, a recent double blind, placebo-controlled trial found that cocaine- and alcohol-dependent users taking disulfiram were most likely to achieve combined abstinence from cocaine and alcohol (Pettinati et al., 2008). Secondary analyses revealed that patients taking a disulfiram-naltrexone combination were most likely to achieve 3 consecutive weeks of abstinence from cocaine and

alcohol. However, disulfiram is reported to be associated with a number of side effects in cocaine dependent users and its use in clinical settings is restrained due to safety concerns. Malcolm et al. (2008) looked at randomised clinical trials that investigated the safety of disulfiram in cocaine-dependent users. The findings showed that disulfiram in trials that eliminated subjects with serious cardiovascular, hepatic, and psychiatric disorders has an acceptable side-effect profile for the treatment of cocaine dependence with or without alcohol dependence at doses of 250 mg/day or less.

Also, the idea of substituting cocaine with another central nervous system (CNS) stimulant which possesses similar pharmacological and behavioural effects but with less abuse potential has recently been gaining attention. Similar to opioid replacement therapy, the goal of stimulant replacement treatment would be to reduce craving and withdrawal and thereby promote abstinence. Findings from a systematic review of randomised controlled clinical trials of the efficacy of a number of CNS stimulants (mazindol, d-amphetamine, methylphenidate, modafinil and bupropion) do not however provide strong support for the use of these stimulants for cocaine dependence (Castells et al., 2007). Nonetheless, some data suggest that these stimulants, especially dexamphetamine and modafinil, could have some therapeutic potential but further research is needed.

The non-amphetamine-type stimulant modafinil, which is prescribed for the treatment of narcolepsy idiopathic hypersomnia and has dopamine- and glutamate-enhancing actions, has been reported to significantly reduce cocaine use compared to placebo controls in a double-blind controlled clinical trial (Dackis et al., 2005). These results were confirmed in a more recent clinical trial investigating the effects of modafinil in treating the dependence of another illicit stimulant drug, namely methamphetamine (Shearer et al., 2009). 80 methamphetamine-dependent subjects were allocated randomly to modafinil (200 mg/day) (n = 38) or placebo (n = 42) under double-blind conditions for 10 weeks with a further 12 weeks post-treatment follow-up. Although there were no group differences in methamphetamine abstinence, craving or severity of dependence, medication-compliant subjects in the modafinil group tended to provide more methamphetamine-negative urine samples over the 10-week treatment period. Overall, outcomes were better for methamphetamine-dependent subjects with no other substance dependence and those who accessed counselling. A number of clinical trials are currently ongoing in the US and in the UK to further investigate the therapeutic potential of modafinil for cocaine dependence.

Finally, there is accumulating evidence suggesting that GABA, the main inhibitory neurotransmitter in the brain, modulates the dopaminergic system and cocaine effects. A recent literature review of clinical trials of the therapeutic potential of GABAergic enhancing drugs reported that baclofen, topiramate, vigabatrin and tiagabine were the most promising in either reducing cocaine consumption, maintaining abstinence or reducing cocaine cravings (Karila et al., 2008).

Immunotherapy

A novel approach to cocaine treatment currently being tested uses the body's own immune system. Once administered, the so-called TA-CD cocaine vaccine induces the production of cocaine antibodies, which bind to cocaine molecules in the bloodstream and prevent them from passing through the blood-brain barrier. Naturally occurring cholinesterases then convert cocaine into inactive metabolites, which are subsequently excreted. By preventing cocaine molecules from reaching the brain, the vaccine blocks the euphoric effects of cocaine and thereby reduces its reinforcing properties and, theoretically, its continued use. Phase I and phase II trials of the TA-CD vaccine's immunogenicity, efficacy and safety have shown reductions in cocaine subjective effects, in cocaine use and retention in treatment (Martell et al., 2005; Kosten et al., 2002). The results of these initial clinical trials are encouraging and further studies are required to test the viability of the cocaine vaccine as a treatment for cocaine-dependence. A phase III multi-site trial is awaiting approval in the US which would involve 300 patients. In Europe, a large joint multi-site trial is about to start in Italy and Spain with several hundreds volunteers.

Psychosocial interventions

The number of psychosocial interventions that have been evaluated properly for the treatment of cocaine dependence is limited. Interventions incorporating cognitive behavioural therapy and contingency management (CM) have yielded the best results so far for the treatment of stimulant-dependence (Dutra et al., 2008; Lee and Rawson, 2008). Similarly, a Cochrane review on psychosocial psychostimulant interventions concluded that consistent, positive behavioural results (retention in treatment, reduction in drug consumption) were only observed in psychosocial interventions that included contingency management as a component (Knapp et al., 2007). CM consists in reinforcing abstinent behaviour positively by rewarding abstinent drug users with incentives, such as vouchers for retail items, contingent on objectively verified abstinence from recent cocaine use.

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Finally, pharmacotherapy is unlikely to provide a 'magic bullet' and a general lesson from the experience of treating other types of drug problem is that they are likely to be most effective if accompanied by appropriate psychosocial interventions and support.

For further information on cocaine, including cocaine treatment, two comprehensive publications are freely available on the EMCDDA's website:

- [Treatment of problem cocaine use – a review of the literature](http://www.emcdda.europa.eu/html.cfm/index18945EN.html)
(<http://www.emcdda.europa.eu/html.cfm/index18945EN.html>)
- [Cocaine and crack cocaine: a growing public health issue](http://www.emcdda.europa.eu/html.cfm/index44746EN.html)
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