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► [The search for medications to treat stimulant dependence.](#)

Kampman K.M.

*Addiction Science and Clinical Practice*: 2008, 4(2), p. 28–35.



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Expert and accessible review of the state of play in finding effective and (to the patients) acceptable medications to initiate or sustain abstinence from cocaine or methamphetamine. Though extensive, the results of this US-led search have so far been disappointing.

**Abstract** Progress in understanding the neurobiology of stimulant dependence has enabled researchers to identify medications whose pharmacological effects suggest they might help patients initiate abstinence or avoid relapse. Several of these medications and a vaccine have shown encouraging results in controlled clinical trials with cocaine-dependent patients, though none has yet been approved in the USA for treating stimulant dependence.

Patients who experience severe cocaine withdrawal symptoms are twice as likely to drop out of treatment and less likely to attain abstinence in outpatient programmes. The most promising medication for initiating abstinence is modafinil, currently approved for the treatment of narcolepsy and itself a mild stimulant. The latest trial involved 210 cocaine-dependent patients who took 200mg or 400mg modafinil daily, or a placebo. Among patients dependent only on cocaine, both dosages of modafinil were superior to placebo for promoting abstinence, but this was not the case among the 41% also dependent on alcohol. Propranolol has also shown promise. For sustaining (as opposed to initiating) abstinence, promising [GABAergic medications](#) include gamma-vinyl GABA (GVG), tiagabine, and topiramate.

Disulfiram (Antabuse) is a promising cocaine relapse prevention medication with a unique mechanism of action. Its effects lead to extremely high cocaine and dopamine levels when cocaine is ingested, making the high less pleasant by increasing associated anxiety. Four published trials have demonstrated that disulfiram reduces cocaine use in cocaine-dependent patients. Another promising option being explored is the 'vaccine' TA-CD. It works by stimulating the production of cocaine-specific antibodies which bind to cocaine molecules and prevent them crossing the blood–brain barrier.

The search for a medical treatment for methamphetamine dependence started more recently. At least one candidate medication has shown promise in early clinical testing. Bupropion is an antidepressant which supports positive mood by inhibiting the reuptake of dopamine into cells, leaving more of the neurotransmitter circulating in the brain. The same mechanism may be helpful in easing the negative mood symptoms of methamphetamine withdrawal. In a recent trial involving 151 methamphetamine-dependent patients, bupropion recipients (especially those whose methamphetamine use at baseline was less intensive) had somewhat better abstinence outcomes compared with placebo.

Treatment approaches combining efficacious medications and proven behavioural interventions will almost certainly produce the best results. Among the latter is voucher-based reinforcement therapy, a form of contingency management which rewards patients who achieve predetermined therapeutic goals with vouchers redeemable for goods and services.

All the trials to date have been relatively small, so the efficacy and safety of these medications has not been definitively established. Also, most have primarily included men. Although no medications are currently proven to be effective, it is hoped that effective pharmacological treatments for stimulant dependence will soon become available.

## FINDINGS

Arguably this useful, accessible and well organised review leans towards a 'glass half full' (and soon may be fuller) interpretation of the evidence. As the author acknowledges, stopping stimulant use is much less of a problem (in fact, it occurs naturally even in dependent users) than staying stopped. The bind relapse-prevention medications are in, is that either they are not effective, or if they are, patients will simply stop taking them once they have recovered from the unpleasant consequences of overdoing stimulants to the point where they want to re-experience the highs. Hence the interest in long-acting solutions such as vaccines; the decision to take these can be made at a time when motivation (or coercive pressure) is high, and they remain a restraining influence when motivation wanes. The hope is that this period will embed the habit of non-use. But even these may require the motivation to repeat the procedure once the vaccine wears off. As [has been remarked](#), if the patient has sufficient resolve to keep taking medications, they are probably also well on the way to succeeding in any sort of treatment, whether or not it involves medications. There is also the risk that other drugs not blocked by the vaccine will be substituted for cocaine.

The featured review argues that psychosocial therapies are inadequate due to high drop-out rates, but the same can be said of medication-based programmes. For the reasons given above, few trials have both retained patients in compliance with the medication regimen, and at the same time restrained their stimulant use. Combining medication with rewards for abstinence and/or complying with treatment can help initiate abstinence, but [it is unclear](#) whether these gains are typically sustained.

Another recent but more technical overall [review](#) of medications for cocaine dependence recently reached similar conclusions. Other recent reviews and [meta-analyses](#) include one of [antipsychotic medications](#) in the treatment of cocaine dependence, which found no evidence to support their clinical use. A similar verdict was reached in respect of

[anticonvulsants](#) and [prescribing other stimulants](#) (a variety of substitution treatment).

Prompted by decades of cocaine-dominated drug problems, development of medications to counter these has [been a top priority](#) for the US government, which has funded the testing of over 60 marketed medications. Though extensive and persistent, the results of this US-led search have so far [been disappointing](#). However, [hopes remain high](#) in some quarters and the search continues. Caution is required because all medications have side-effects, and some of those currently being considered for treating stimulant dependence can have severe consequences. Until risks and costs are clearly balanced by benefits, doctors and patients cannot be advised to consider routine use of any of the candidate medications. In the meantime, [European clinicians](#) prefer to rely mostly on psychosocial interventions to reduce cocaine-related problems.

Last revised 10 July 2009

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