


## analysis

This entry is our analysis of a study considered particularly relevant to improving outcomes from drug or alcohol interventions in the UK. The original study was not published by Findings; click [Title](#) to order a copy. Free reprints may be available from the authors – click [prepared e-mail](#). [Links](#) to other documents. [Hover over](#) for notes. [Click to highlight](#) passage referred to. [Unfold extra text](#)  The Summary conveys the findings and views expressed in the study. Below is a commentary from Drug and Alcohol Findings.

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### ▶ [A double blind, placebo controlled trial of modafinil for the treatment of cocaine dependence without co-morbid alcohol dependence.](#)

Kampman K.M., Lynch K.G., Pettinati H.M. et al.

**Drug and Alcohol Dependence: 2015, 155, p. 105–110.**

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*Modafinil is a mild stimulant which it is hoped might plug the gap in effective pharmacotherapies for dependence on cocaine. Though this trial found that it promoted abstinence from cocaine, others have not, and its inconsistent benefits have been seen as failing to outweigh the drug's side effects.*

**SUMMARY** No medications are yet approved by US authorities for the treatment of cocaine dependence. Modafinil is a mild stimulant approved in the USA to treat narcolepsy and shift-work sleep disorder, which may also help treat cocaine dependence by reducing withdrawal symptoms, craving, and cocaine-induced euphoria.

In line with this potential, modafinil has been found to reduce cocaine use among cocaine-dependent patients in clinical trials. In one [of these trials](#), across all 210 patients modafinil was not superior to placebo in promoting abstinence from cocaine. However, it was superior among those not also dependent on alcohol, suggesting that it may only be effective when cocaine dependence is not accompanied by dependence on alcohol.

Consequently, the featured trial evaluated 300 mg daily of modafinil among 94 cocaine-dependent patients not also dependent on alcohol, drawn from 174 cocaine users seeking treatment at the University of Pennsylvania's Treatment Research Center in the USA. The centre recruits patients through media ads as well as through professional referrals.

Subjects dependent on any drug except cocaine, nicotine or cannabis were excluded, as were those with serious psychiatric conditions. The 94 in the trial averaged 47 years of age and were typically African-American men who smoked cocaine in the form of crack. On average they had used cocaine on 12 days in the month prior to treatment and for 12–13 years.

After a week during which pre-treatment measures were obtained and psychosocial treatment began, patients were allocated at random to be dispensed either modafinil or placebo weekly over the following eight weeks. Their attendance at the clinic for twice-weekly urine tests, for treatment (including weekly individual cognitive-behavioural therapy) and research assessments



#### Key points

From summary and commentary

Modafinil is a mild stimulant approved to treat pathological sleepiness which has been tried with generally negative results in the treatment of dependence on stronger stimulants.

The featured trial found that it promoted abstinence from cocaine among patients who were generally smoking crack cocaine but not dependent on any other drug, except perhaps nicotine or cannabis.

Inconsistent benefits in curbing cocaine use have not been seen as outweighing the drug's side effects.



was incentivised by a **contingency management** procedure; for each treatment visit attended, participants could draw for prizes worth up to \$100.

The primary outcome measure was use of cocaine during each of the eight weeks, assessed by urine tests and questionnaire responses. Patients were considered abstinent during that week if both biweekly urine tests were negative and they reported no cocaine use. Any indicator of cocaine use led the whole week to be declared non-abstinent. Other weeks when neither classification could be made were weeks when data was missing.

## Main findings

Of the 94 patients, 70 completed the eight weeks of the trial, averaging 12–13 visits to the clinic out of a possible 16, missing just over a fifth of urine tests, providing cocaine-use data for six to seven of the eight weeks, and taking around 90% of their prescribed pills. On none of the measures of compliance and retention did the two sets of patients substantially or **significantly** differ. There were, however, some clear differences in cocaine use.

Across various ways of accounting for weeks when data was missing (ignored; treated as non-abstinent weeks; or treated as non-abstinent if the individual had not yet left treatment), patients dispensed modafinil were between 2.2 to 2.5 times more likely to be abstinent. Only when all missing weeks were counted as non-abstinent weeks was the ratio (diminished to about 2.2) not statistically significant, but by a small margin. Missing data made little difference to how modafinil compared with a placebo.

Another measure assessed complete abstinence over the last three weeks of the trial, confirming modafinil's advantage. Even when missing weeks were counted as non-abstinent, the difference of 23% abstinent on modafinil versus 9% on placebo was statistically significant.

Placebo patients were more likely to be assessed as experiencing craving for cocaine, but there were no substantial or significant differences in withdrawal symptoms. Except for psychiatric problems (during the eight weeks, fewer modafinil patients experienced these), problems related to substance use were not significantly less common among modafinil patients. Though both patient and practitioner were unaware which substance was being taken, in weekly assessments modafinil-treated patients were nearly twice as likely to be rated by their clinicians as "very much improved" and nearly three times more likely to rate themselves very much improved – the latter a statistically significant difference.

Modafinil was well tolerated. Adverse events were mainly mild and generally evenly distributed between the modafinil and placebo groups. Non-significantly more modafinil-treated subjects reported insomnia (21% v. 6%) and anxiety (15% v. 4%). Mild and transient elevations in blood pressure possibly attributable to study medication were noted in six modafinil patients, but none dispensed a placebo.

## The authors' conclusions

In now three trials, modafinil has demonstrated efficacy among cocaine-dependent patients without alcohol dependence. Although concurrent use of cocaine and alcohol is common, current alcohol dependence is estimated to be present in only 30% of cocaine-dependent patients in the USA and lifetime alcohol dependence in about 60%, meaning modafinil could be effective for many cocaine-dependent patients.

In the current trial, among cocaine-dependent patients not also dependent on alcohol, at 300 mg daily modafinil was superior to placebo at promoting abstinence from cocaine, craving for cocaine was attenuated, and modafinil patients were more likely to see themselves as very much improved. This is the second trial in which modafinil was found superior to placebo on the predefined primary cocaine use outcome across all the patients in the study, not just in a sub-group. However, results among cocaine-dependent patients not also dependent on alcohol have been inconsistent. The main difference between the featured trial and a **negative trial** was that in the featured trial patients were more likely to complete treatment and took more of their medication, possibly because the incentives to comply were more persuasive, and possibly too because the dose of modafinil (300 mg rather than 200 or 400 mg daily) struck a better balance between being tolerable and being effective.



**FINDINGS COMMENTARY** The difference of 23% abstinent on modafinil versus 9% on placebo over the last three weeks of the trial both makes the case for and against modafinil. It improved on an inactive placebo, but still left three-quarters of patients using the cocaine it was hoped the drug would help them leave behind. These results were achieved when compliance with taking the medication was strongly incentivised, and may not apply in usual practice which generally lacks such incentives, or persist once incentives have ended, and were achieved at the cost of side effects experienced by a substantial minority of patients.


Also, though the overall pattern of reported results is persuasive, there are question marks over two key findings. Across the eight weeks of treatment, when missing data was treated as indicative of cocaine use – [previously considered](#) by the same research team as the most appropriate strategy – the results fell short of statistical significance. It means that arguably on [what was originally](#) the study's primary measure, its results were inconclusive. Only after the results were in was the more convincing difference relating to the final three weeks of the trial [mentioned](#) among the intended analyses, meaning that the possibility cannot be eliminated that it was chosen 'after the event' because (perhaps by chance) it showed modafinil in the best light.

Other trials have also been short-term, with results confined to treatment phases lasting up to 12 weeks. Apart from the featured trial and a [small pilot trial](#) from the same research team with a similar type of caseload, across entire samples studies have generally not found modafinil significantly effective in the treatment of cocaine dependence. [Neither](#) has it proved effective in treating dependence on the similar stimulant, methamphetamine. If modafinil is effective, it seems to be so only in very specific circumstances. More on these studies [below](#).

In the featured study and others, psychosocial support was equalised for placebo and modafinil patients. A trial of optimised and more intensive support versus lesser support supplemented by modafinil, with equality of resources allocated to both, would give a clearer picture of whether the medication is sufficiently effective to displace psychosocial therapy as the dominant response to dependence on cocaine. No such study has yet been done.

Even if modafinil were effective against stimulant dependence, any gains in this respect would at least be partially offset by unpleasant side effects among a substantial minority of patients. Outside these trials and when used for other complaints, some side effects have been so severe that in 2010 the European Medicines Agency [said](#) the drug's benefits only outweighed its risks for the treatment of very serious sleepiness attracting a diagnosis of narcolepsy; more [below](#).

### Other trials generally negative

The same research team had also [previously found](#) modafinil effective in treating dependence on cocaine, but similar studies by the same team and by other US research teams have produced negative findings. A partial exception was a [study](#) in which statistically significant effects were seen among patients who were not and never had been dependent on alcohol, but not among the remainder of the sample, a differential effect which would have to be confirmed in a trial designed for this purpose before it could be considered robust. In other trials which excluded patients with a history of dependence on alcohol, or those currently dependent on alcohol, modafinil has not proved effective, suggesting that this finding is an unreliable guide to who might benefit from the medication. [Unfold](#)  [the supplementary text](#) for more on these studies.

 [Close supplementary text](#)

The featured study followed an encouraging [small pilot trial](#) from the same authors conducted at the same centre and with a similar type of caseload (but just 62 patients). As in the featured study, treatment lasted eight weeks, but the dose was 400 mg a day rather than 300 mg for the patients randomly allocated to modafinil. Relative to a placebo, during the eight weeks abstinence from cocaine was substantially elevated among modafinil patient, perhaps partly because there were 12% more missing urine tests (counted as non-abstinent) among the



placebo patients. The difference in the proportion of cocaine-free tests was 18% (42% on modafinil, 24% placebo), so two-thirds of this difference could have been due to missed tests. Modafinil's advantage was no less among patients who were still using cocaine in the run-up to starting treatment versus those who did not. The latter had a better prognosis, a [common finding](#). There were no serious adverse events and no medication-associated dropouts.

The earlier [negative trial](#) referred to in the featured study is of considerable interest because it was conducted at the same clinic, by largely the same team of researchers, for eight weeks also, with the same kind of psychosocial support, and with what looks like a very similar caseload, in both cases excluding alcohol-dependent applicants (and those with any other form of dependence except on nicotine, or nicotine or cannabis). Patients were randomly allocated to a placebo or to 200 or 400 mg modafinil daily. Despite an initial advantage, over the eight weeks there was no significant difference in cocaine abstinence rates, though generally modafinil retained a small advantage. Proportions achieving three weeks of continuous abstinence were very similar at around a third. During the final three weeks, this measure non-significantly favoured the 400 mg patients – a much smaller difference than in the featured study of 11% versus 4% on a placebo. Again, side effects were more frequent in the modafinil patients. In this study all the patients had to test positive for cocaine at the start, not the case in the featured study, which may for that reason have recruited a more treatment-ready caseload better able to make the most of modafinil.

These results are even more surprising because there was a reason why modafinil should have seemed better in this study than in the featured study – the relatively poor retention of the placebo patients (61–62% completed treatment on modafinil versus only 50% on placebo). Poorer retention contributed to [more](#) missed urine tests, which were counted as uniformly positive for cocaine. In contrast, in the featured study retention was almost exactly the same on placebo and modafinil, perhaps due to greater incentives to stay in treatment.

Looking back on this study and speculating on why its results differed, the authors of the featured study instead saw reinforced compliance with treatment as favouring modafinil. In the earlier trial 61–62% of patients completed treatment versus about 76% in the featured trial; if modafinil was effective, greater retention would have meant a greater chance to show this. They thought another possibility was that the featured study hit on the right compromise between a dose high enough to prevent cocaine use and one so high it caused deterrent side effects – 300 mg a day versus 200 or 400 mg. Another possibility is that though modafinil is generally effective or generally ineffective, by chance in these two studies the outcomes fell either side of the threshold for statistical significance.

The drug was also not effective to a statistically significant degree in [another large US study](#), which also randomly allocated patients to a placebo or 200 mg or 400 mg of modafinil daily, but this time over 12 weeks. Across the entire sample, the study's primary yardstick of success – the proportion of days on which tests indicated non-use – yielded no advantage for modafinil, though these patients managed to sustain their abstinence for a longer maximum duration – 12–13 days versus nine. Applicants for the study had to test positive for cocaine in the period immediately before treatment, indicative of a less treatment-ready caseload perhaps less able to make the most of modafinil than in the featured study.

However, significant findings emerged when the sample was divided up into the roughly 40% who had at some time been dependent on alcohol and the remainder who had not – modafinil resulted in lower cocaine use among those not now and never alcohol-dependent, but not among those with a history of dependent drinking. Modafinil's advantage among patients without a history of alcohol dependence seemed to have emerged even



before treatment started and was already fully fledged in the first week, casting some doubt on whether this was an effect of the drug. Also, the analysis was not planned in advance so **could have** capitalised on the fact that samples can be sub-sampled in any number of ways until one (perhaps purely by chance) results in a significant finding. In this study as in others, any advantages gained in curbing cocaine use were at the cost of modafinil's unpleasant side effects, experienced by a substantial minority of patients prescribed 400 mg a day.

Two other US trials from a different research team and conducted in Texas found modafinil ineffective in treating cocaine dependence, and that retention even in short-term treatment was poor (1 2). Both had excluded study applicants who were currently dependent drinkers, but not those who had been in the past. **One of these trials** directly tested whether modafinil was differentially effective among the generally more treatment-ready patients who had already stopped using cocaine before treatment started; no such effect was found.

Preliminary results **have been released** from a study led by the researchers responsible for the featured trial, involving patients dependent on both cocaine and alcohol. Over 13 weeks the number of weeks during which patients tested abstinent from cocaine was virtually identical on modafinil and on placebo, perhaps reinforcing their contention that the drug works best among patients not also dependent on alcohol.

A review which found 11 studies and amalgamated their results **has confirmed** the impression from the studies described above that relative to a placebo, "there is no evidence to conclude superiority of modafinil in increasing cocaine abstinence and treatment retention rate".

Modafinil has also been tried in the treatment of dependence on a stimulant similar to cocaine – methamphetamine. Over 12 weeks, the **US study** allocated 210 methamphetamine-dependent patients to a placebo or to 200 mg or 400 mg modafinil daily. Among other criteria, patients had to have never been dependent on alcohol and to have used methamphetamine shortly before treatment started. Typically they were white men in their 30s and 40s who used methamphetamine on over 60% of days. They were offered relatively intensive (three times a week) group therapy. Only just over half completed treatment and only 16% tested abstinent from methamphetamine in the final two weeks. On no measure of substance use, and only sporadically on other measures, were there any differences between the three sets of patients. The modafinil patients did however suffer from significantly more complaints which might have been related to the drug.

 [Close supplementary text](#)

## Safety concerns

As a stimulant, there must be concern that patients dependent on another stimulant will become dependent on modafinil and 'misuse' it for the same purposes they used cocaine – that it will become 'part of the problem' rather than the solution. In practice this risk **is limited** (but not eliminated) by modafinil's slow onset of effects after oral administration and its chemical unsuitability for smoking or injecting – similar properties to those which make methadone a therapeutically effective substitute for heroin. Modafinil **affects different** neurochemical systems to those affected by cocaine or methamphetamine, possibly also accounting for its lesser attraction as

 The drug is, however, not risk-free. In the UK **recognised use** of

modafinil is limited to excessive sleepiness extreme enough to be diagnosed as narcolepsy, in line with a [recommendation](#) made in 2010 by the European Medicines Agency that the drug's benefits only outweighed its risks for the treatment of this condition. Though treatment of dependence was not specifically mentioned, in the opinion of the agency's expert committee, "For all other indications [conditions for which it might be prescribed] ... the risk for development of skin or hypersensitivity reactions and neuropsychiatric disorders outweighed the evidence for clinically important efficacy. Therefore, the Committee concluded that all other indications should be withdrawn from the marketing authorisations of these medicines."

In contrast to most of the studies described above and guidance in Europe and specifically in the UK, a [review](#) of modafinil's use for the treatment of cocaine dependence found that no adverse effect was significantly more common (though several were substantially more common) in patients allocated to modafinil than those allocated to a placebo. However, this data seems to derive from a count of studies in which these effects occurred rather than a count of the number of patients who experienced them. The studies reviewed above generally found several possible side effects much more common among modafinil than placebo patients. But in the context of these tightly controlled and short-term trials, serious adverse events were rare.

Set against any risks of modafinil must be the risks posed by cocaine dependence of the kind resistant to psychosocial approaches. Modafinil offers a possible equivalent to methadone for heroin dependence – a milder and legal medication with similar effects to the substance on which the patient has become dependent. Given that dependent cocaine use is not safe in itself, if modafinil moderates cocaine use when safer alternatives have failed, the risks may be worth it. At the moment however, this seems doubtful.

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