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► [Randomized controlled trial of dexamphetamine maintenance for the treatment of methamphetamine dependence.](#)



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Longo M., Wickes W., Smout M. et al. [Request reprint](#)
Addiction: 2010, 105(1), p. 146–154.

Australian researchers trialled a new form of what is often seen as a 'controversial' treatment – prescribing (in this case, long-acting) amphetamine to stabilise amphetamine dependent patients. The patients stayed in treatment nearly twice as long and their dependence remitted more than when prescribed a placebo.

Summary For the first time this study tested the impact of a long-acting form of [amphetamine](#) as medication to help control dependent use of the closely allied stimulant, methamphetamine. Prescribed more usually for the treatment of pathological sleepiness or attention deficit/hyperactivity disorder, effects of the amphetamine tablets prescribed in the study take several hours longer to emerge than normal amphetamine and last three to six hours longer, giving it a 'smoothing' profile similar to methadone for heroin users; non-rapid onset make it less intensely pleasurable, and longer duration suits it to once-daily administration. Doses in the study averaged 80mg per day and were capped at 110mg.

To ensure as far as possible that the medication was the active ingredient in the outcomes of the trial, a randomly allocated [control](#) group was prescribed an identical placebo tablet and patients, staff and researchers gathering the data did not know who had been prescribed which. Also the requirement to attend daily for supervised tablet-taking meant researchers knew how much of the medication had actually been consumed, and all patients were offered the same psychosocial support and treatment contact. The trial started with up to a fortnight during which doses of the active tablets (with a mirror procedure for the placebos) were titrated upwards, followed by an intended 12 weeks on the stabilised dose and then four weeks when it was tapered to zero and the trial treatments ended. For about the first month patients had to go daily to

the clinic pharmacy to have their tablet-swallowing supervised by staff; after this supervision was continued but at community pharmacies.

Patients were recruited from the South Australia state addiction treatment service. Among other criteria, to be included in the trial they had to be dependent only on methamphetamine and not on any other drug except tobacco, to have recently used methamphetamine regularly, and to be free of serious physical or mental illness. Of 313 screened initially over the phone, 49 started the trial, of whom 23 were allocated to amphetamine and 26 to placebo. Nearly 9 in 10 were injecting their methamphetamine, usage averaged five days a week, patients averaged 32 years of age and had been using for over ten years, half were unemployed, and half too had previously been treated for their use of the drug. Patients were assessed by researchers at the start of the trial, during the treatment period, and two months after this period ended, a follow-up giving some indication of whether impacts might persist once patients were no longer taking medication. Though many patients dropped out of treatment, at the final follow-up researchers managed to re-assess nearly 8 in 10 methamphetamine patients and nearly two thirds of the placebo patients. Patients were included in the outcome analyses regardless of whether they were able to be reassessed.

Main findings

The most clear-cut and statistically significant result was greater retention among patients prescribed the active medication. Two thirds completed the trial compared to just under third prescribed placebo, they stayed in treatment for an average 86 days (out of a possible 104) compared to just 49, and placebo patients dropped out earlier.

The other statistically significant differences related to signs of dependence rather than use levels. In both groups, patients' responses to the [Leeds Dependence Questionnaire](#) revealed an easing of their dependence from the start to the end of treatment. Two months later this easing had been sustained among those prescribed methamphetamine while dependence rose (but not to pre-treatment levels) among those prescribed placebos. The gap this created at the final follow-up was statistically significant. Withdrawal symptoms too were suppressed more effectively by methamphetamine than placebo throughout the treatment period, a greater reduction which was statistically significant during the initial two weeks of treatment.

During treatment estimated consumption of methamphetamine (an amalgam of times used and amount used on each occasion over the past month) fell dramatically in both groups, a drop largely sustained at the final follow-up. However, these reductions were only slightly and non-significantly steeper among the methamphetamine patients. These results based on the patients' own accounts were broadly confirmed by testing hair samples.

Of the 23 patients prescribed amphetamine, one experienced a serious side effect – high blood pressure requiring a dose reduction. On average systolic blood pressures actually fell during amphetamine prescribing, while other measures of circulatory health were stable. No serious mental health problems were recorded, and in particular there were no reports of psychotic symptoms, though some patients did experience mild irritability, mood swings and headaches. There was an appreciable weight loss among the prescribed patients not seen in the controls.

The authors' conclusions

The primary objectives of this study were to engage users in treatment and reduce methamphetamine use and dependence. The results showed that a maintenance pharmacotherapy programme of daily sustained-release amphetamine dispensing under pharmacist supervision is both feasible and safe and improves engagement with treatment as assessed by retention. Also dependence was moderated more by methamphetamine than placebo. Together with the general decreases in methamphetamine use, dependence and withdrawal symptom severity, these outcomes provide preliminary evidence that sustained-release amphetamine may be an efficacious treatment for methamphetamine dependence.

The fact that (except for retention) methamphetamine's advantages over placebo were minor and/or not statistically significant may have been due to the relatively intensive support both groups were offered including psychotherapy, medical and research appointments, and daily monitoring by pharmacy staff. Patients said this structure greatly helped reduce their methamphetamine use. However, 43% of the sample did not attend any psychotherapy sessions, suggesting that counselling alone may not be enough to engage a high proportion of methamphetamine injectors in treatment.

FINDINGS Methamphetamine is a potent and for predisposed individuals, highly addictive variant of the stimulant amphetamine, known in its smokable form as 'ice' or 'crystal' among other names. While blood levels of the active metabolites of cocaine fall to half their peak level in 90 minutes, methamphetamine's 'half-life' is 10 hours or more. Users tend to take the drug in 'binges' or 'runs' over one to three days, followed by abstinence, then repeated use. Because of its lengthy half-life, this pattern results in increasing concentrations of the drug which can be toxic, particularly because the body does not 'get used' to its effects as readily as with other drugs. When experts met to rank drugs in terms of their harms in the British context, they placed methamphetamine fourth after alcohol, heroin and crack cocaine, though in terms of harms to the actual user it came third, closely behind heroin and crack. On this sub-scale, amphetamine and cocaine came next after alcohol.

In [England and Wales](#) it has been estimated that 319,000 adults used amphetamines in 2009/10 and of whom 110,000 used in the past month, and in [Scotland](#), about 3805 and 1268. Across the UK in 2009/10 or 2010, at least 12,128 people using amphetamines (including methamphetamine) were in or referred for treatment for problems with illegal drugs, just over 5% of the total of 226,302. These totals are an amalgam of differently defined statistics in the different nations. Details in [background notes](#). How many of these patients were prescribed amphetamine is not recorded, but from the featured study and the studies summarised below it would seem a minority would both be suitable and benefit from this prescribing more than they would have done from psychosocial therapy alone.

But without prescribing on offer, many fewer patients see treatment as 'for them', so fewer put themselves in a position to benefit from psychosocial therapy. They also miss an opportunity for harm reduction advice and professional monitoring of physical and mental health, both important for amphetamine users. Prescribing also helps retain patients long enough and stabilise them sufficiently for them to gain the most from these other inputs, and has important direct harm reduction benefits associated with reduced injecting.

Controlled trials have tested stabilisation rather than maintenance programmes. Typically amphetamine prescribing programmes are likely to be shorter than those for opiate dependent patients, partly because stimulants can more easily be withdrawn; a typical untreated pattern of stimulant use includes periods when users are able (or feel they have to) stop using for a while. However, British services have prescribed long-term and observed beneficial results in terms of client stability and reduction in injecting. Concerns over cardiovascular risks from heavy stimulant use and the risk of precipitating a psychotic episode cannot be dismissed, but from the studies to date these risks are largely confined to patients who top up their prescribed doses with large amounts of illegal supplies, the risks are probably less than in untreated stimulant dependence, they can be minimised by careful monitoring, and patients' health is improved in other ways by a stabilised lifestyle, reduced injecting, and the regular medical contact associated with attending for prescribing and dispensing.

These impressions from clinical experience and studies which have observed the progress of patients have yet to be confirmed in rigorous trials which have as far as possible equalised everything (including randomising patients and the taking of 'dummy' tablets) except the prescribed amphetamine. In the three randomised trials to date including the featured study, substantial and statistically significant benefits were generally not found, but all three were as justifiably seen as stabilisation-withdrawal trials as maintenance, and probably none was representative of the usual patients and usual practice observed by less rigorous studies.

About the featured study

As much as to amphetamine prescribing, the dramatic improvements seen in the featured trial seem a testament to the motivation of this highly selected set of patients and to other elements of the treatment package. Prescribing did substantially extend retention, but was more the 'icing on the cake' than the main influence on continued methamphetamine use, dependence and withdrawal symptoms. Unusually for a maintenance programme, improvements were largely sustained after patients left treatment, perhaps aided by their continuing care at the service from which they had been recruited.

Where amphetamine did have a statistically and possibly clinically significant advantage was in the severity of persisting dependence two months after treatment ended. Such an advantage during treatment would have been unsurprising, since reliance on illicit supplies would have been attenuated by the prescription. That it persisted suggests the prescribing may have had an indirect effect via longer retention in treatment and the longer period when patients' lives were regulated by daily attendance, leading to a more lasting and extensive normalisation of their relationships with methamphetamine. This finding emerged from a comparison which was not planned in advance, so requires confirmation by other studies designed from the start to test this possibility.

The absence of psychotic symptoms is important given concerns over temporary psychotic states precipitated by high doses of amphetamine (so-called 'amphetamine psychosis'). In other studies, these episodes have occurred, but generally only among patients also heavily using illegal stimulants. Presumably such episodes were absent in the featured study because the methamphetamine patients did not continue to use their customary illegal doses of methamphetamine 'on top' of their prescribed amphetamine.

Weight loss over this short period was quite steep among the prescribed patients, but this is not typical of similar studies or of experience in Britain.

One major benefit not reflected in the study's measures must have been that the number of injections was substantially reduced as patients cut down on their methamphetamine use, presumably greatly reducing the risks of injection-related damage and infectious diseases.

Better retention and the other more modest differences between amphetamine and placebo groups seem plausible effects of maintenance prescribing. But despite a strong randomised and blinded methodology, there are reasons to believe that these might not have been entirely due to the medication, and also reasons to query the applicability of the findings beyond the presumably highly motivated caseload attracted by the study. For more ► [background notes](#).

UK guidelines

Britain's tradition of amphetamine prescribing was deprecated in 2007 by [national clinical guidelines](#). Partly due to limitations of the available research, these concluded that, "Even though there may be individual patients for whom existing treatment should be continued for the time being, substitute stimulant prescribing does not have demonstrated effectiveness and, accordingly, should not ordinarily be provided".

[Guidelines](#) from the British Association for Psychopharmacology were less dismissive of the message from studies to date, which despite their inadequacies consistently "suggest benefits in terms of reduction in [amphetamine] use and in injecting". Both guidelines agree that whatever the medication, it takes second place to psychosocial interventions, seen as the mainstay of treatment strategies for stimulant using patients.

The British experience

In comparison with other countries, Britain has a rich history of amphetamine prescribing and of studies of this practice. Studies are summarised below – details in [background notes](#).

The [first British study](#) concerned (mainly) injectable methamphetamine prescribed during the late 1960s in London to 23 young patients who had typically used amphetamine for less than a year. Only three stayed in treatment beyond three months. The authors' verdict that amphetamine substitution was a therapeutic failure [remained influential](#) for 20 years until the advent of AIDS and acceptance of harm reduction as a public health strategy. Local UK reports from later years involving older addicts and oral medication often dispensed under supervised consumption were more positive, and also generally reassuring on the issue (often described as "controversial") of whether such prescribing risks psychotic episodes – as [one reviewer](#) put it, "the most serious potential adverse consequence of dexamphetamine replacement therapy".

None of the studies could stand up to methodological scrutiny, but together they painted a consistent and persuasive picture of in-treatment progress, though not of whether this was sustained after treatment. Generally they reported substantial benefits in reduced injecting and illegal drug use, crime and risk of infection, though in some studies absolute abstinence and totally crime-free lives were rare. Prescribing attracted more problem amphetamine users in to treatment, so extended these benefits to a greater proportion of the potential caseload. Carefully controlled prescribing did not in itself

cause psychotic episodes, though these did happen in a few patients who also took large doses of illegal stimulants, especially when they had a history of such episodes. Psychotic episodes may have been less frequent than if the patients were not in treatment and will also have been more readily identified by clinicians and treated.

In 2004 these conclusions were questioned by publication of the [only UK trial](#) to rigorously test amphetamine prescribing by randomly allocating amphetamine-dependent patients to this plus a psychosocial treatment package, or to the same package, but without prescribing. Only such a study can securely attribute any improvements to the medication, as opposed to differences between patients or other elements of treatment. It found no substantial or statistically significant benefit associated with prescribing; with or without the tablets, both groups reduced their illegal amphetamine use and their rates of injecting to roughly the same degrees. Similar conclusions emerged from the Australian randomised trial ([▶ below](#)), but neither was a test of what is usually considered 'maintenance' as opposed to a short, fixed period of stabilisation followed by withdrawal.

The obvious explanation for the UK results is that previously reported benefits were methodological artefacts which disappeared once the scales were more adequately evened up in a randomised trial. However, for several reasons the trial was not a definitive verdict on the (non-)value of amphetamine maintenance. Among these are that the focal and comparison treatments were not typical of normal practice, and the probability that the patients (especially the barely more than half left in the study at the final two assessments) were highly selected and not representative of potential patients.

International experience

For a slightly extended version of this section [▶ background notes](#). A [US reviewer](#) has usefully summarised the concerns about prescribing amphetamine to amphetamine-dependent patients. Prime among them are cardiovascular problems and psychotic episodes. As long as good psychosocial therapy was available and there was appropriate monitoring, he judged these and other risks "likely manageable" and less than the risks run by untreated stimulant users.

A team including the researcher who led the trial described below [have advised](#) that substitution therapy is most appropriate for severely dependent, daily amphetamine injectors. The most enduring benefits are likely to be achieved in combination with psychosocial intervention; prescribing attracts, stabilises and retains, while the therapy helps extend and embed lifestyle change preparatory to discharge, which seems to occur more often and earlier than in opiate substitute programmes. Screening and monitoring for psychotic symptoms are essential, and some clinicians do not consider the treatment suitable for patients with a history of schizophrenia or bipolar affective disorder. Partly to avoid diversion on to the illicit market, but also to determine whether maintenance is worth continuing with, supervised consumption, urinalysis and regular medical monitoring for side effects are advised for at least the first three-month stabilisation period.

Sydney in Australia was the location of the [first trial](#) to rigorously test dexamphetamine prescribing for amphetamine dependence by randomly allocating patients to this treatment (daily supervised consumption of oral medication for 12 weeks including a final two weeks withdrawal) plus counselling, or to counselling alone. However, at 10 weeks, this trial cannot be considered a test of what most people would consider a maintenance programme as opposed to stabilisation prior to withdrawal. There were no statistically significant differences in outcomes, but the differences that there were (in use of illegal amphetamine, spending on these drugs, injecting, and infection risk behaviour) favoured the prescribed group. Counselling attendance and retention records seemed indicative (as other studies have typically found) of the poor pulling power of counselling alone,

and the potential for substitute prescribing to work synergistically with counselling by improving attendance.

Thanks for their comments on this entry in draft to Richard Pates of the Cardiff School of Health Sciences. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

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