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▶ Efficacy of opiate maintenance therapy and adjunctive interventions for opioid dependence with comorbid cocaine use disorders: a systematic review and meta-analysis of controlled clinical trials.

Castells X., Kosten T.R., Capellà D. et al. Request reprint

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About a third of Britain's heroin dependent patients also have problems with crack cocaine. Can opiate substitute prescribing help with both problems, and which special anti-cocaine therapies are worth adding on? This review trawled the international research for the answers.

Abstract A team of Spanish and US authors sought to assess whether programmes such as methadone maintenance (aimed primarily at controlling illicit opiate use) can also curb the accompanying cocaine/crack use seen in about half of patients. If the core maintenance therapy and/or special add-ons can be effective against cocaine, the result should be to improve the relatively poor heroin use, crime and social outcomes associated with co-use of the drug.

The aim was not just to review the research but also to combine its results in meta-analyses to determine which approaches had the best record. Included were studies available in any language up to September 2007 which randomly allocated opiate maintenance patients who also used cocaine either to the treatment being tested or to a comparison approach. For technical reasons, and because these were thought to represent meaningful improvements, the primary yardsticks of effectiveness were how many of the patients sustained continuous heroin or cocaine abstinence confirmed by urinalysis. Also analysed when available were the proportions of tests free of cocaine or heroin use markers, and retention in treatment.

In all, 37 relevant articles were found documenting research whose subjects were mostly men in their thirties and early forties and nearly all dependent on both heroin and cocaine. Studies were categorised in to those testing the core maintenance treatment,

and those testing supplementary interventions targeting cocaine use; these two types of studies are summarised separately below.

Optimising the core maintenance intervention

No studies were found which tested opiate maintenance against no treatment or against an inactive placebo drug, but six did test variations of maintenance prescribing. Three of these studies enabled an assessment of the impact of low versus higher doses of maintenance medications. Across these studies, higher doses significantly increased retention, the proportion of patients who sustained heroin abstinence, and the proportion of heroin-free urine tests, but there was no significant impact on either indicator of cocaine use.

Across the four studies to test this, at equivalent doses methadone substantially and significantly outperformed buprenorphine (these are the two main maintenance medications) in enabling more patients to sustain abstinence from cocaine. It also increased retention and (but non-significantly) improved heroin abstinence on both measures.

Supplementary interventions targeting cocaine use

The issue addressed next was the impact of adding a cocaine-oriented therapy to the core maintenance programme. Of these 34 studies, 20 tested medications. Across the relevant studies, the only class of drugs shown to significantly help patients stay free of cocaine (both in terms of sustained abstinence and the proportion of cocaine-free urines) were those which raise brain levels of a neurotransmitter (dopamine) thought responsible for some of the pleasurable effects of cocaine, and which becomes depleted after regular use of the drug. These medications included bupropion, amphetamine, disulfiram, and mazindol. They also improved retention in treatment and, prescribed as a supplement to methadone, increased the proportion of patients sustaining abstinence from heroin.

Additionally there was tentative evidence (from just two studies) that desipramine, a drug which acts on a different neurotransmitter system, also helps patients sustain cocaine abstinence. Other medications were not shown to have improved substance use outcomes and one class of drugs (GABAergic agonists such as tiagabine and gabapentin) was associated with significantly shorter retention in treatment, possibly due to aversive side effects.

Of the psychosocial interventions, contingency management has been the most studied and has the best record. Typically these interventions systematically applied rewards (such as shopping vouchers) and/or sanctions in response to the results of urine tests for cocaine and/or heroin use. When cocaine was the sole drug targeted, the effect was to substantially and significantly raise cocaine abstinence rates on both measures and also to increase the proportion of heroin-free tests. In contrast, rewards/sanctions targeting both heroin and cocaine were generally ineffective. This pattern of results probably reflects the fact that stopping cocaine use in response to the rewards is easier than stopping heroin use. In the few studies which tested these approaches, contingency management allied with cognitive-behavioural therapy improved sustained cocaine abstinence rates, the therapy on its own narrowly failed to have a significant impact, while acupuncture affected neither retention nor the proportion of cocaine-free urines.

It seemed that the effective interventions (drugs which raised dopamine levels; contingency management) were most effective among patients starting treatment rather than established patients, but this proposition had not been tested within a single study.

Authors' conclusions

The authors said their analyses showed that among dual heroin and cocaine dependent patients, higher doses of maintenance medications improved heroin use outcomes without affecting cocaine use. Methadone outperformed buprenorphine on sustained cocaine abstinence, retention in treatment and (narrowly non-significantly) heroin use measures. High-dose methadone was the most effective combination of drug and dose, possibly because it best helps patients stop using heroin, which also helps divorce them from circles within which cocaine is traded. However, the relative safety of buprenorphine and its suitability for primary care settings may make it preferable in clinical practice, and dose adjustments beyond those tested in the reviewed studies may alter its effectiveness relative to methadone. Of the supplementary interventions targeting cocaine, evidence of an impact on cocaine use was strongest for contingency management (especially when cocaine was the sole drug targeted), and for medications which raise brain dopamine levels.

FINDINGS In 2005/06, 25% of patients in drug treatment in England were there primarily to address problems involving both crack cocaine and opiates like heroin. By 2008/09, the figure had risen to 30%, in numbers a rise from about 21,000 to nearly 25,500 patients. In Scotland this combination is far less common; instead benzodiazepines are the dominant drug accompanying heroin. In 2009, just 7% of patients starting treatment for heroin addiction in Scotland said they also used crack cocaine. These and similar patients in the other nations of the UK are candidates for the interventions assessed by the featured review.

Routine monitoring statistics cited above have been supplemented by national studies. In 2006 researchers attempted to recruit and then track the progress of a representative sample of patients starting drug treatment in England. Of these, 44% had used crack in the four weeks before seeking treatment. While it seems all or nearly all these felt their crack use was a problem, just 1 in 8 (12%) of treatment-seekers considered it their primary problem. For the bulk of problem crack users, the drug was subsidiary to their heroin use, the type of patient investigated by the studies in the featured review. This was also the case in Scotland among patients starting addiction treatment (other than in prison) in 2001 and 2002. Though in the past three months around 30% each had used crack or cocaine powder, this was rarely their main drug and most did not see their use as a problem. Given that 9 in 10 of all patients had used heroin and that for the vast majority this was seen as their main problem drug, it seems likely that cocaine was usually subsidiary to heroin use.

In the English study, after a few months in treatment only 15% of crack users recalled receiving a crack-specific intervention, and whether they had was unrelated to whether crack use ceased or continued. Despite this lack of targeted attention, crack users did as well as anyone else in terms of short or longer-term retention in treatment, in employment, increase in legitimate income, accommodation, and increase in the proportion of parents living with all their children. If anything, crack seemed easier to

give up than heroin; 53% of crack users had stopped using by the first follow-up and 61% by the second, respectively 9% and 12% higher than the corresponding figures for heroin and heroin users. The implication is that while there was considerable scope for therapeutic enhancements to tackle crack use among opiate-dependent patients (enhancements which the featured review sought to identify), the core treatments offered these patients were in themselves accompanied by substantial improvements.

In terms both of size and reliability, the strongest anti-cocaine impacts identified by the featured review were associated with contingency management programmes applying rewards and punishments for cocaine abstinence/use. Such programmes have the potential to create a cocaine-free period during which other ways of coping and sources of pleasure can become established. Typically however studies have tracked patients only while the rewards are being applied. These in-treatment gains generally do not persist or have not been shown to persist, and there is concern that intrinsic motivation can be undermined if patients see themselves as 'just doing it for the prizes'. There are also ethical concerns about the aggravation of inequality if the most dependent patients find themselves unable to achieve the rewards, and about paying people to do what they 'should' be doing anyway – complying with the law and with programmes to safeguard and improve their health.

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