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► **Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence.**

Mattick R.P., Breen C., Kimber J. et al.

Cochrane Database of Systematic Reviews: 2014, 2, art. no.: CD002207.



Authoritative analysis of clinically relevant trials of buprenorphine versus methadone maintenance for heroin dependence confirms that buprenorphine has less 'holding power', and that among patients who are retained, there are equivalent reductions in illegal drug use. But is methadone's 'stickiness' an advantage or a liability?

SUMMARY Oral methadone and sublingual (absorbed under the tongue) buprenorphine are the main medications prescribed long-term (on a 'maintenance' basis) to patients to substitute for heroin and other opiate-type drugs on which they have become dependent. Substituting legal [opioids](#) in known doses and purity provides an opportunity to stabilise the patient by eliminating withdrawal, craving, participation in obtaining illegal opioids, and injecting.

This updated review for the Cochrane Collaboration, one of the world's most trusted sources for research analyses, included 31 trials totalling 5430 participants compared to the 24 and 4497 of the 2008 version. It focused on studies which allowed clinicians to adjust the dose depending on how the patient has reacted; these more closely reflect actual and [recommended](#) clinical practice than fixed-dose studies.

The review sought trials which had [randomly](#) allocated patients dependent on heroin or allied drugs to buprenorphine maintenance, versus either a placebo or maintenance on methadone. Where possible, results of similar studies were statistically pooled. Of the 31 trials, 15 were from North America and nine Europe. Most (22) were reportedly 'double-blind', meaning neither patients nor clinicians were told which preparation the patient was taking. When methadone was compared with buprenorphine, concealment entailed requiring all patients to take two preparations, one the active medication, the other a placebo version of the second medication. Urine tests results were based on the number of tests [indicative](#) of continuing illegal heroin use. [Editor's note: All else being equal, the method used in the review favoured preparations which do less well at retaining patients in treatment and which therefore offer less scope for patients to accumulate tests indicative of continuing illegal drug use. Another common method is to assume missed tests would have indicated a return to drug use, favouring medications which best retain patients.]

Main findings

Dosing levels were flexible in 11 studies which compared the two medications. Across these, the chances of a patient leaving treatment during [study periods](#) ranging from six weeks to a year was 17% lower on methadone. This means for example that if 60 out of 100 patients are retained on buprenorphine, had they instead been prescribed methadone, typically another 12 would have stayed in treatment. Results were similar and more consistent across the five double-blind studies in which neither patients nor clinicians were told which medication the patient was taking. Among the remaining six non-blinded studies, methadone's retention advantage was not quite statistically significant and varied considerably between studies.

Across the eight flexible-dose studies which provided this data, numbers of urine tests indicative of continuing heroin use only slightly and non-significantly favoured buprenorphine. The same was true for the patients' own accounts of their heroin use. There were also no significant differences in use of cocaine or benzodiazepines, though in both cases there was a slight advantage for methadone. Just two studies contributed to the analysis of criminal activity, cumulating to no significant difference between the medications.

In the fixed-dose studies which compared buprenorphine with methadone, retention was only significantly different (patients stayed longer on methadone) in the low-dose comparisons of less than 16mg of buprenorphine versus less than 40mg of methadone. In no dose range did one medication versus the other result in significantly fewer urine tests or self-reports from the patients indicative of heroin use.

Across the 11 studies which compared buprenorphine to a [placebo](#), buprenorphine in whatever dose range retained patients better in treatment. However, only high-dose (at least 16mg per day) buprenorphine led to fewer urine tests indicative of continuing illegal heroin use.

Among all 31 studies, the few to compare rates of unwelcome possible side effects found no differences between buprenorphine and placebo or methadone, with the exception of one study which found more methadone than buprenorphine patients experienced sedation.

The authors' conclusions

Broad practice implications remain unchanged from 2008. Buprenorphine is an effective medication, bettering a placebo on retention, and in high doses also in urine test results indicative of continued heroin use. Prescribed at flexible doses, superior retention means methadone should be the default maintenance medication, with buprenorphine reserved for situations where higher dose methadone is not possible, for patients who do not react well to methadone, or to provide patient and clinician choice. Though both medications suppress illegal heroin use, on this criterion they did not significantly differ. Despite these findings, buprenorphine may have advantages in some settings and under some policies where its relative safety and ability to be taken every other day are particularly useful.

Findings in respect of consequences which take time to become noticeably different, including mortality, adverse side effects and crime, may have suffered from the typically short duration of randomised trials.

FINDINGS COMMENTARY The analysts' verdict was that given adequate doses, methadone was the more effective treatment, but not by such a margin that buprenorphine could positively be advised against. Greater retention was the key advantage – important, because over the periods represented in the studies, when patients leave, relapse to dependent illicit opiate use is the norm. When (as in normal practice in Britain) patients and clinicians choose either medication, the retention advantage of methadone [has been](#) much greater than in trials where patients accept being randomly allocated. Perhaps partly because patients who want this choose buprenorphine, and partly due to its opiate-blocking properties, while in treatment patients who opt for the drug also use illegal opiates less often (1 2), a contrast to the equivalence found across randomised trials.

The analysts' rider that buprenorphine might be offered simply to create choice is more important than the minor mention warranted in a review of studies in which patients did *not* have a choice. Choice is [likely to help](#) engage and retain patients in treatment who want

or expect different things from their medications. In [one English study](#), the consequences of a mismatch between user preferences and service policies was visible in the early drop-out of would-be patients denied buprenorphine, which many valued for [what they saw](#) as its superior opiate-blocking properties. Buprenorphine's better safety profile and its attraction for a less severely affected caseload commend it particularly to primary care settings; in [Birmingham](#) for example, it was twice as likely to be prescribed as a maintenance drug by GPs as by specialist addiction services.

Randomised but still not a level playing field

Limitations in the featured analysis and in the flexible-dosing studies it relied on introduce considerable uncertainty over the meaning of the findings. Some of these limitations probably meant methadone's advantage would have been greater in everyday practice. Even when in many studies they could have got methadone elsewhere, patients were prepared to accept allocation to an unfamiliar medication. Possibly they were keen on trying a new medication with less strong opiate-type effects. In most of the studies they were (compared to UK caseloads) either early in their addiction or treatment careers, relatively young, or relatively socially included. One of the questions marks over buprenorphine is its suitability for more dependent, high-dose heroin users.

Also perhaps disadvantaging methadone was the way the urine test comparison was calculated. This appears to have ignored missed tests rather than treating them as positive (shorter retention means buprenorphine patients probably missed more) and to have credited to buprenorphine results from patients who avoided positive tests by switching to methadone.

On the other hand, buprenorphine patients too might have been disadvantaged. The drug permits non-daily dosing and perhaps an earlier shift to unsupervised consumption. For many patients, this offers a more attractive regimen than daily supervised methadone. The key studies sacrificed these advantages to 'blind' patients and staff to which drug was being taken.

NICE verdict

Since it drew on this data, these sources of uncertainty were also incorporated in an [assessment](#) for the UK's National Institute for Health and Clinical Excellence (NICE), which itself added further layers of uncertainty. It found that methadone's retention advantage in flexible-dose studies translated in to slightly greater improvements in (largely health-related) quality of life. Since methadone also resulted in lower health care costs, it was judged more cost-effective than buprenorphine.

For the featured reviewers, similar findings meant methadone should be the default choice, but experts and advisers convened by NICE put a [different spin](#) on largely the same evidence. Their advice was that the choice between the medications should be made "case by case", based on issues like whether buprenorphine's safety was a priority in that individual case, whether the patient was aiming to withdraw from opiate-type drugs altogether (easier with buprenorphine), and patient preference. When for an individual the medications were equally appropriate, methadone might take precedence because it cost less and on average extended the benefits of being in treatment. [UK prescribing guidelines](#) take a similar line.

Neither the Cochrane nor the NICE assessment fully accounted for the cost-savings and convenience possible due to buprenorphine's extended action and relative safety, such as being able to allow more unsupervised dosing. These are not just theoretical, but [have been taken advantage of](#) in Britain. Also not fully accounted for were the ways in which buprenorphine might further enhance quality of life. However, neither did the assessments fully account for the benefits of greater retention on methadone.

How to choose?

Uncertainty about overall advantage, allied with differences in the safety and effects of the drugs and feasible dispensing arrangements, suggest that some patients will be best suited to methadone, others to buprenorphine. Unfortunately, there is little in the research to indicate who will be in which camp. Buprenorphine possibly helps depressed patients more than those not suffering depression, while patients dependent on large doses of opiates may find it inadequate because there is a ceiling beyond which higher doses do not augment opiate-type effects. Patients who value the 'wrapped in cotton wool' feeling typical of heroin are [likely to prefer methadone](#); those who value a clearer head might prefer buprenorphine. Patients aiming for a relatively rapid break from all opiate-type drugs might do best to opt for buprenorphine initially, or to switch to it after stabilising on methadone, but have to accept the risk that instead they will drop out and return to dependence on illegal drugs.

Methadone is likely to remain the mainstay of maintenance prescribing due to its wider appeal to patients and lower cost, but the case for considering buprenorphine is strong and may get stronger if potential cost savings are further realised, and as methadone's major advantage – greater retention – comes to be seen as an impediment to leaving treatment. Until recently, in Britain retention for 12 weeks was the prime benchmark of effective treatment and partly determined local funding. Now the emphasis ([1 2](#)) is on moving patients through and out of treatment to (it is hoped) secure recovery via social reintegration. In line with policy, 'successful' treatment exit [features strongly](#) as a goal in 'payment by results' commissioning criteria in England. Against this backdrop, buprenorphine's ability to help patients take a half-step away from reliance on opiate-type effects and its greater 'leavability' could become valued more, while methadone's 'stickability' is being seen not (or not only) as a strength, but a liability. However, buprenorphine's leavability is itself a liability if it means (as in this [British study](#)) that many more patients drop out and still only a small minority leave after successful detoxification.

The previous version of the review was analysed by Finding on the basis of an [extended analysis](#) of the eight flexible dose studies then available. This still seems a valid basis for assessing the review's implications. None of the three new to the current version were among the double-blind studies which constitute the most stringent comparison of the two medications prescribed flexibly. In [one](#) retention actually meant completing treatment while in prison, another was a [small German study](#) which found retention about equal, and the last was a [Norwegian trial](#) which was arguably an invalid comparison because methadone doses could vary while buprenorphine was fixed at 16mg.

For clinical guidance on how to use buprenorphine see [UK prescribing guidelines](#) and a [review from three leading US researchers](#).

Thanks for their comments on the original entry to Tom Carnwath, then consultant psychiatrist at the Tees, Esk & Wear Valleys NHS Trust in England. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

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