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International review and UK guidance weigh merits of buprenorphine versus methadone maintenance

An analysis of the most clinically relevant studies of buprenorphine versus methadone maintenance treatment of opiate dependence has confirmed that buprenorphine has slightly less 'holding power', but that among patients who are retained, there are equivalent reductions in the illegal use of opiate-type drugs. The findings informed new UK guidelines on the treatments.

FINDINGS The comparison between flexible-dose sublingual (absorbed under the tongue) buprenorphine and oral methadone was one of several made in the updated review[1] for the Cochrane Collaboration, one of the world's most trusted sources. Where possible, results of relevant studies were statistically pooled. The analysis is important because studies which allow clinicians to adjust the dose depending on how the patient reacts more closely reflect actual and recommended clinical practice[2] than fixed-dose studies.

Across the eight studies (see background notes for citations and further information), 18% more methadone than buprenorphine patients remained in treatment for time periods varying from six weeks to a year. This means, for example, that if 60 out of 100 patients were retained on buprenorphine, had they instead been prescribed methadone, typically another 11 would have stayed in treatment. Retention over at least these periods is key because when patients leave, relapse to dependent illicit opiate use is the norm.

Among the studies which provided this data, numbers of positive urine tests (indicative of continuing illegal opiate 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 or in crime.

IN CONTEXT The analysts' verdict was that given adequate doses, methadone was the more effective treatment, but not by an overwhelming margin. However, limitations in their analysis and in the source studies it relied on introduce considerable uncertainty.

Some of these (fuller discussion in background notes) may have meant that methadone's advantage would be greater in everyday practice. Even when 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 all but one 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 disdavantaging 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. However, most studies sacrificed these advantages to 'blind' patients and staff to which drug was being taken. Blinding also (because the patient might have been on methadone) caused unnecessary delays in reaching optimal doses of buprenorphine. Both considerations may have diminished retention on buprenorphine.

Since it drew on this data, these sources of uncertainty were also incorporated in a recent assessment[3] for the UK's National Institute for Health and Clinical Excellence (NICE), which itself added adding 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 more cost-effective than buprenorphine. However, the analysis did not explore all the ways in which buprenorphine's costs might be (and are being[4]) reduced such as unsupervised dosing, nor all the ways in which it might enhance quality of life. Neither did it fully account for the benefits of greater retention on methadone.

PRACTICE IMPLICATIONS For clinical guidance on how to use buprenorphine see UK prescribing guidelines[2] and a review from three leading US researchers.[5]

For the Cochrane team their findings meant methadone should be the default maintenance medication, with buprenorphine reserved for environments or patients where high dose methadone is not possible. Their reasoning was that at high or flexible doses, "methadone is associated with better suppression of heroin use", yet their review concluded this was *not* the case for flexible dose programmes. They added that in some settings, buprenorphine may be advantaged by its relative safety and alternate-day dosing option, a rider which opens the door for the drug when daily supervised consumption would otherwise be required or take-home doses are desirable, and perhaps in some primary care practices.

Experts and advisers convened by the UK's National Institute for Health and Clinical Excellence (NICE) put a different spin[6] 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[2] take a similar line.

Neither assessment fully accounted for the cost-savings and convenience possible due to buprenorphine's extended effects and relative safety, the latter (as Scottish guidelines[7] point out) particularly applying to tablets which combine buprenorphine and naloxone. This formulation reduces the risk of the tablets being crushed and injected. The result could be to facilitate more primary care-based treatment and to reduce the need to control diversion to the illicit market by insisting on supervised consumption.

Uncertainty about overall advantage, allied with differences in the safety and effects of the drugs and possible dispensing arrangements, suggest that the most defensible conclusion is that some patients will be most 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 and 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 may prefer methadone, those who value a clearer mind might prefer buprenorphine.

In England around the years 2005 and 2006 buprenorphine accounted for over a quarter of patients prescribed opiate substitutes, having rapidly gained ground over the previous years. Though dispensed more often as take-home doses, surveyed[8] patients were less likely to use other opiate-type drugs 'on top' than with methadone and were also more likely to be satisfied with their treatments. Methadone is likely to remain the mainstay of maintenance prescribing due 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 realised and if methadone's major advantage − greater retention − comes to be seen as an impediment to successful treatment exit.

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

1 **FEATURED STUDY** Mattick R.P. et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database of Systematic Reviews: 2008, 2.

2 Department of Health (England) and the devolved administrations. Drug misuse and dependence: UK guidelines on clinical management. Department of Health [etc], 2007.

3 Connock M. et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. Health Technology Assessment: 2007, 11(9).

4 Best D. et al. National prescribing audit: an assessment of prescribing practices for opioid substitution treatment in England, 2004–2005. National Treatment Agency for Substance Misuse, 2007.

5 Johnson R.E. et al. Buprenorphine: how to use it right. Drug and Alcohol Dependence: 2003, 70(2, suppl.), p. S59–S77.

6 National Institute for Health and Clinical Excellence. Methadone and buprenorphine for the management of opioid dependence. NICE technology appraisal guidance 114. National Institute for Health and Clinical Excellence, January 2007.

7 Scottish Medicines Consortium. Buprenorphine/naloxone 2mg/0.5mg, 8/2mg sublingual tablet (Suboxone).

Scottish Medicines Consortium, 2007.

8 Gordon D. et al. The 2007 user satisfaction survey of tier 2 and 3 service users in England. National Treatment Agency for Substance Misuse, May 2008.

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