Effect of buprenorphine dose on treatment outcome.

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How much buprenorphine does it take to keep patients in treatment and suppress illicit use of heroin or other opiate-type drugs? This review concludes that on average higher is better than lower, but that individualising dose and a preparedness to go high if needed are the keys to effective treatment.

Summary As an alternative primarily to methadone, buprenorphine has many qualities which make it an effective treatment for opioid dependence. There is less of a build up of tolerance to the drug, it is safer in overdose, and it may help relieve negative mood. Induction is easy, even for physicians with limited experience with opioid maintenance treatment. Several studies have found buprenorphine a safe and effective medication for primary care-based treatment.

Most of the initial studies of buprenorphine reported that lower doses (8mg or less per day) were not as effective as higher doses (8–16mg) in suppressing illicit opiate use and retaining patients in treatment. Such findings led to studies of yet higher doses which have found 16 –32mg safe and more effective than lower doses in reducing illicit use and craving for opioids.

Doses greater than 24 to 32mg per day do not directly increase the risk of overdose death due to respiratory depression but may increase risk when other depressant drugs are taken at the same time. The aim is to achieve the best treatment outcome without jeopardising safety.

As a contribution to this objective, the featured review looked for studies which would enable a comparison between retention and substance use outcomes among patients prescribed less than 16mg per day versus those prescribed 16mg or more. The search was restricted to randomised controlled trials of buprenorphine maintenance treatment, the results of which were published in English-language articles between 1960 and 2010. Fifty such articles were found of which the results reported in 21 could be included in a synthesis of the findings. These studies were divided in to those which prescribed 16mg or more of buprenorphine per day versus those which prescribed less than 16mg per day.

Main findings

The raw figures were that in the higher dose studies 69% of patients completed treatment compared to 51% in lower dose studies. This difference remained statistically significant when other influences on retention were taken in to account. Among these was a negative relationship between retention and the proportion of urine tests the study found positive for illicit opioids.

In higher dose studies patients were less likely to test positive for illegal opioids. Positive tests were also less likely in studies which retained more patients in treatment, but more likely in studies with relatively high rates of cocaine-positive tests. When all these influences were considered together, dose was no longer related to opioid-positive urine tests but the other associations remained statistically significant.

The authors' conclusions

This analysis provides strong evidence based on 21 randomised trials that doses of 16mg or more a day can improve retention in buprenorphine maintenance treatment. Retention is in turn associated with less frequent use of illicit opiate-type drugs. These results suggest that dose may play an important role in improving treatment outcomes for buprenorphine maintenance patients. Clinicians should consider prescribing 16mg or more per day to patients who do not do well on lower doses, especially if they express an intense craving for opioids. Some may be reluctant to do so for fear that certain patients will 'divert' some of the dose to the illicit market. In these cases they could first order a urine test to confirm whether the patient is taking their buprenorphine. The cost of this test and the cost of the higher doses may be barriers to high-dose provision for some patients and some treatment providers, but not prescribing a high enough dose could increase the risks of relapse and of dropping out of treatment, increasing social costs overall.

The results of the review should however be placed in the context of the caseloads being prescribed to. Most earlier studies involved patients addicted to illegally obtained heroin, but modern caseloads include patients addicted to opioids prescribed in the course of legitimate medical practice. For the latter, lower doses may be as effective as higher doses among the former. In other words, what is an ineffectively low dose for one patient may not be for another. Not just the final dose but also the speed of dose adjustment during buprenorphine induction needs to be individualised to improve treatment outcome without jeopardising safety. Because of this the results of different studies may reflect not just the final stabilisation dose, but also how quickly this was reached.

FINDINGS The pattern of the findings suggests that higher dose suppresses illegal use of opiate-type drugs largely because it improves retention in treatment. However, the article does not specify whether missed tests were treated as if they had indicated illegal use. If they were, more missed tests due to shorter retention on lower doses would automatically tend to worsen the urinalysis record, even if tests actually taken by patients while they remained in treatment indicated that illegal use was no more likely.

Rather than comparing high- and low-dose patients in the same studies, the featured analysis compared results from studies which prescribed high doses with those which prescribed low doses. As the authors comment, this confounds differences due to dose with differences due to other features of the studies. An alternative approach is not to compare absolute levels of retention and illicit substance use at different doses, but the degree to which these better a placebo. This was the approach taken in the relevant review for the Cochrane collaboration, which found that across all relevant studies, only doses of 16mg or more a day convincingly improved suppression of heroin use relative to a placebo. In this analysis it seems missed tests were simply ignored rather than treated as if they had indicated illegal use.

'Completion' in the studies included in the featured analysis meant staying in treatment for at most just under a year and usually six months or less. Up to this point it is generally accepted that patients are still consolidating the lifestyle changes made possible by maintenance. If high doses extend retention well beyond this point, the question arises more sharply whether on balance this is a good thing because it prevents relapse to regular illegal use of opiate-type drugs and stabilises lives, or a bad thing because it keeps patients dependent on their legal supplies instead of 'moving on' and out of treatment, even if for some this will mean life-threatening relapse. See this Findings analysis for more on this issue and how an expert UK group sought to reconcile the tensions.

UK guidance says 12–16mg of buprenorphine daily is sufficient for most patients, but acknowledges that some need up to 32mg. Based on limited research, World Health Organization guidelines say higher doses are likely to result in better retention and less heroin use than lower doses, with minimal adverse consequences other than cost. If patients are continuing to use illicit opioids, consideration should, the WHO experts said, be given to increasing doses up to 32mg daily.

Individualisation of dose is essential as the effective dose varies widely. For example, in one Australian study which adjusted the dose to how well patients responded, some were adequately maintained on 2mg a day, while others required 32mg. A similar range was found in a US study which adjusted dose in response to patients' scores on a systematic assessment incorporating their illicit opiate use, clinic attendance, withdrawal symptoms and signs of toxicity. Best practice is not necessarily high-dose buprenorphine, rather titrating dose to the lowest which prevents cravings and use on top, maximising efforts to help patients change their lifestyles for the better.

Policies which go further and encourage across-the-board dose restrictions undermine the effectiveness of buprenorphine maintenance as they do of methadone maintenance. These policies may reflect a lingering aversion to maintenance prescribing, and associated prioritisation of getting patients off opioids, or they may reflect cost considerations. Patients too sometimes resist the doses they actually need to avoid illegal use because of an ambition to cease opioid use altogether or because of feared side effects. When these desires lead relapse-prone patients to take low doses, the result is likely to be continued risk from illicit opiate use and early drop-out from treatment. In respect of buprenorphine, the concerns which motivate low doses are less salient because high doses do not correspondingly increase the risk of overdose and because the medication is relatively easy to withdraw from. After being stabilised on adequate doses, patients who want to attempt treatment termination do not face a hurdle has high as that posed by withdrawal from high-dose methadone.

Thanks for their comments on this entry in draft to Duncan Raistrick of the Leeds Addiction Unit in England. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

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