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This entry is our account of a review or synthesis of research findings selected by Drug and Alcohol Findings as particularly relevant to improving outcomes from drug or alcohol interventions in the UK. Entries are drafted after consulting related research, study authors and other experts and are © Drug and Alcohol Findings. Permission is given to distribute this entry or incorporate passages in other documents as long as the source is acknowledged including the web address http://findings.org.uk. However, the original review was not published by Findings; click on the Title to obtain copies. Links to source documents are in blue. Hover mouse over orange text for explanatory notes. The abstract is intended to summarise the findings and views expressed in the review. Below are some comments from Drug and Alcohol Findings.

▶ Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence.

Mattick R.P., Breen C., Kimber J. et al.
Cochrane Database of Systematic Reviews: 2009, 3, Art. No.: CD002209.

A surprisingly small basket of randomised controlled trials (but one confirmed by other studies) supports the superiority of methadone maintenance over detoxification for patients prepared to be allocated to either option.

Abstract This update of a review first published in 2002 incorporates studies available for analysis up to the end of 2008. It adopted the rigorous Cochrane review process to analyse randomised controlled trials which compared methadone maintenance against treatments for opioid dependence which did not involve a similar (ie, opioid replacement) therapy. Comparison treatments may for example have been detoxification, drug-free rehabilitation, or placebo medication, or comparison patients may have been on a waiting list for methadone maintenance. The question addressed was whether patients dependent on heroin-type drugs do better when offered methadone as a long-term substitute medication, than when not offered any form of long-term substitute prescribing.

Eleven relevant studies were found involving altogether 1969 participants. All seven studies for which retention could be analysed found patients stayed longer in methadone than in comparison treatments. Among the four newer studies published since 2000, without methadone typically 15% of patients were retained for the periods measured in the studies; with methadone, 68%. Retention is of little use unless accompanied by improvements in targeted outcomes. Here the clearest finding was in relation to biological tests indicative of continuing use of illegal heroin. All six studies reporting this outcome found lower use rates on methadone, combining to an estimate that typically 70% of patients not offered methadone maintenance test positive, a figure reduced to 46% by methadone. Largely the same set of studies also asked patients how often they had used heroin. Generally their answers confirmed the reductions found by hair or urine tests, but with considerable variability across studies.

Across just three studies which reported on crime, there were substantial relative reductions in patients allocated to methadone which just failed to reach statistical significance. Similarly across the four studies which reported on deaths, which were halved among the methadone patients.

The analysts observed that patients have withdrawn from trials when assigned to a drug-free programme, so randomised trials have generally compared methadone maintenance with placebo 'methadone' or with methadone-based detoxification. These trials show that methadone (usually allied with services such as counselling, psychosocial therapy, medical services and often psychiatric care) can reduce the use of heroin in dependent patients and retain them in treatment. Beyond these trials, a broader international literature confirms methadone's impact on heroin use, crime and mortality, and on HIV infection and behaviours (such as sharing injection equipment) which risk infection.

FINDINGS It is important to understand the limited questions which can be answered by the randomised trials in the featured review. These demonstrated the impact of methadone maintenance among patients who were prepared to accept allocation to this treatment or to an alternative, or who had opted for methadone but had to wait. In terms of comparing one approach with another, the most such studies can do is show which is preferable when either seems appropriate and is acceptable to the patients, at least to the degree that they are prepared to countenance random allocation. Such studies cannot demonstrate which is the preferable option overall. There will be other patients determined to opt for detoxification or set against methadone maintenance, for whom methadone would be unacceptable or clearly unsuitable; still others would not join such studies because they want to be sure of a maintenance treatment and/or feel in no position to make a success of detoxification. Considerations like this probably explain why none of the comparisons involved residential rehabilitation. Caseloads suitable for non-residential substitute prescribing, and those suitable for residential drug-free services, would normally overlap so little that random allocation would simply be unacceptable, or would have to be limited to just a few highly selected patients.

Also the trials afforded only a limited range of outcome measures; too few recorded wellbeing and social reintegration measures (important to current policy in the UK) for these to be analysed by the review. The degree to which non-drug related services such as counselling and case management contributed to the outcomes is unclear. Strong patient preferences, and ethical prohibitions against denying patients an effective treatment to find out just *how* effective it is, are among the reasons why randomised trials comparing methadone maintenance against no treatment or non-drug treatments are rare, and often date back decades to when maintenance was experimental and the benefits were unclear. But as the featured study comments, there are many other non-randomised trials which confirm that the benefits found in randomised trials are replicated in more real-world conditions.

None of the trials included in the review were from the UK. Since in Britain most methadone maintenance is provided outside prison (for prison studies see an earlier review analysed by Findings), and at least some form of alternative treatment is normally available, the most relevant studies concern community programmes in which methadone is one of several active treatments on offer. From this perspective, the background notes on this entry detail the individual studies in the review. This more fine-

grained view suggests that retention, crime and mortality gains were probably underestimated, and finds evidence of reduced illegal opiate use not incorporated in the featured analysis. Summary below.

With respect to retention in treatment, two studies clearly demonstrated the superiority of maintenance over detoxification plus aftercare and another (conducted in Sweden and not included in the analysis) that there are patients who simply will not accept further drug-free treatment but will accept, remain in, and benefit from methadone maintenance.

This was one of the studies which clearly demonstrated reduced illegal opiate use among patients allocated to methadone maintenance. In this and in another study in Thailand, patients had repeatedly relapsed after previous detoxifications. Possibly they were poor candidates for a further attempt and prime candidates for a maintenance option. Among first-time detoxification triers earlier in their addiction careers, the results might have been different. However, there are two other (both US, one not included in the analysis) studies which did not specifically recruit patients with a history of unsuccessful detoxification, yet still found maintenance reduced heroin use more effectively than detoxification.

In two of the three studies used to assess crime reductions, the impact of methadone was probably substantially greater then could be incorporated in the analysis. Another study set in Hong Kong was not included, but did find convictions were halved among maintenance patients compared to those unknowingly detoxified from methadone and then prescribed a placebo.

The most dramatic indication of the lifesaving potential of methadone was provided by a Swedish study, where typically four years later four of the 17 patients offered only drug-free treatments (which all refused) were dead, but none of the 17 offered methadone maintenance. This was somewhat, but perhaps falsely, countered by a study in Honk Kong, in which the impression of a higher death rate among methadone patients was possibly due to their staying in touch with treatment and with the study far longer than detoxified patients.

As the featured study comments, among the other benefits of methadone maintenance and allied treatments are that they consistently and significantly reduce the risk of transmission of blood-borne viruses and curb the spread of HIV. This was the prime reason why in 2005 the World Health Organization added methadone (and buprenorphine) to its *List of Essential Medicines*, though the argument for doing so also documented its crime reduction and treatment retention qualities. 'Essential medicine' status reflects not just the effectiveness of the treatment among patients recruited to it, but also the fact that methadone maintenance is capable of widespread implementation and the engagement of a large proportion of the at-risk population in treatment. This conclusion was boosted by an analysis for the European Union which found methadone maintenance cost-effectively prolongs and improves the lives of a population of opioid injectors by averting HIV infections, and that the cost of doing so is typically below the cost of treating the infections, creating health service savings. Importantly, the mathematical model used in this analysis showed that as the proportion of local drug users engaged in treatment increases, costs per averted infection dramatically decrease, and benefits across all drug users in or out of treatment escalate. This is because the treatment is capable of removing a large proportion of drug users from the networks who share injecting equipment, leading to a form of 'herd immunity'.

Thanks for their comments on this entry in draft to David Best of the University of the West of Scotland. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

Last revised 07 November 2009

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