

Fortnightly Review

Methadone maintenance treatment in opiate dependence: a review

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This paper examines the changes and advances in research and clinical practice and examines the role of treatment structure and programme characteristics in the delivery of methadone maintenance. Methadone prescribing has become much more available over the past decade, both in countries with a history of its use, such as the United Kingdom and Australia, and in countries around the world which previously had not endorsed substitute prescribing.¹ There is a need to examine closely the framework in which this treatment is delivered to ensure that the modes of delivery most effective from both cost and benefit perspectives are utilised. This review focuses entirely on methadone maintenance because this is the most extensively evaluated and most used treatment, with about a quarter of a million drug misusers receiving methadone treatment globally. A small number of experimental diamorphine and buprenorphine substitute programmes are being evaluated in several countries.

Most studies have come from the United States and focus on the long term use of methadone in a specific setting; in contrast, methadone treatment in the United Kingdom has received virtually no formal evaluation to date bar one study.² There is concern that a considerable amount of the methadone prescribing could be having little impact on illicit drug use or risk taking behaviour³; a recent study of drug users in police custody echoes this.⁴ The Advisory Council on the Misuse of Drugs has recommended a shift to a more structured approach for delivery of oral methadone maintenance.

The organisation and regulation of methadone maintenance treatment varies widely, with explicit guidelines for programme operation in the United States and Australia and a virtual absence of structure and regulation in Britain. It is likely that policy analysts and treatment providers in countries with high levels of regulation and structured programmes will press for reduction in constraints, whereas settings such as Britain with minimal structure will move in the direction of more formalised delivery systems.

BENEFITS OF METHADONE MAINTENANCE PROGRAMMES

The possible benefits of methadone maintenance prescribing range from impact on illicit opiate use and injection related risk taking behaviour to reductions in the level of criminal activity and other positive social changes. The most important active ingredient of treatment has been debated⁵—whether it is simply the provision in a controlled manner of a strong opiate or whether the counselling and programme structures are the key ingredients promoting change.

Summary points

- Methadone maintenance treatment is probably the most evaluated form of treatment in the field of drug abuse treatment and continues to arouse professional and political controversy
- Possible benefits of oral methadone treatment range from impact on illicit opiate use and injection related risktaking behaviour to reductions in the level of criminal activity and other positive social changes
- The most important active ingredient of treatment has been debated: is it simply the provision of a strong opiate in a controlled manner or is it the counselling and programme structures that are the key ingredients promoting change?
- There is clear evidence that programmes may vary substantially in their efficacy
- Programme factors include dosage of prescribed methadone, maintenance versus abstinence, and support services
- Operational issues include monitoring the use of non-prescribed drugs, diversion of methadone, use of other psychoactive drugs, and oral versus injectable methadone

Treatment evaluation

Carrying out rigorous research in the field of illicit drug use is difficult and as a result reports are sparse. Methadone maintenance is the most researched of the available treatments, however, and an overall assessment of its effectiveness can be made with more confidence than for other treatments.

Four randomised controlled trials have been conducted in which comprehensive methadone maintenance has been compared to a control condition over a substantial period of time.⁶⁻⁹ Two of these trials compared methadone maintenance with no treatment,^{8,9} and the other two were double blind, placebo controlled studies that compared methadone and a placebo, with comprehensive support services available to all participants.^{6,7} All of these trials found that on several measures (illicit use of opioids, involvement in crime, mortality) methadone maintenance was vastly superior to control conditions. Two more recent studies have used randomised designs, comparing methadone maintenance with gradual withdrawal with methadone¹⁰ and prescribing methadone without

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support services with controls on a waiting list.¹¹ Though both these studies describe a shorter duration of treatment they support the role of methadone as a key component of the treatment package.

Taken together, the randomised studies of methadone maintenance show consistent positive results over vastly different cultural contexts (United States, Hong Kong, Sweden, Thailand) and over more than two decades of research. These findings have been supported by some observational studies with some degree of control which have surveyed large samples of opioid dependent individuals who have enrolled for treatment in the United States.¹²⁻¹⁷

OPIOID USE AND CRIME

Ward *et al* have recently reanalysed the findings of the major clinical trials of methadone to assess the size of the effect in relation to illicit opioid use and crime.¹⁸ In one trial included in their analysis Dole and Joseph compared methadone maintenance in New York City in 1969 with a no treatment control and found at 12 month follow up that even on the most stringent criteria of "intention to treat" (that is, rigorously accounting for the composition of the group that did not receive methadone treatment) that subjects in the control group were 92 times more likely to be using heroin daily than were those in the methadone group, and they were 53 times more likely to have been reincarcerated.¹⁹

Several observational studies have confirmed that methadone maintenance has a major impact on illicit opioid use and criminal activity of programme entrants: reduction in opioid use and crime was related to duration in treatment, and longer involvement in treatment was associated with continued reduction in crime.^{12,14,15,19-25} Crime is reduced but not eliminated, and the reduction is greater in some types of drug related crime. Criminality continues, albeit at dramatically reduced rates. Ball and Ross noted the variation of programmes' impact on criminal behaviour and pointed out that methadone maintenance programmes have not specifically focused on patients' criminality.¹² There is scope for developing the crime reduction elements of methadone maintenance programmes. Good links are then needed between the criminal justice system and treatment approaches linked to methadone maintenance. The probation and prison services remain an important source of referral and a trigger to stimulate drug misusers' contact with treatment services.²⁶

INJECTION RELATED RISK TAKING BEHAVIOUR

Evidence is accumulating that the prescribing of oral methadone is associated with lower rates of HIV infection for patients during treatment (O Blick and L Grönbladh, 4th international conference on AIDS, Stockholm, 1988).²⁷⁻³¹ Reductions in risky injecting and sharing behaviours during methadone treatment have been reported.^{12,27,33-35} Programme staff need to recognise that even in the most effective programmes a quarter of patients will continue to inject, albeit less frequently, and therefore sterile injecting equipment should be available.⁸¹

Factors affecting response to methadone maintenance

The capacity of different programmes to achieve significant reduction in illicit drug use varies greatly. This may be due to characteristics of the patients or the programme. Ball and Ross have highlighted the importance of the organisation and the characteristics of the treatment being delivered.¹² Treatment variation will be substantially influenced by overall national policy on the management of opiate addiction.^{18,36,37}

PATIENT CHARACTERISTICS AS PROGNOSTIC INDICATORS

There are no good criteria for prognostic indicators for drug treatment. Patients with good psychosocial adjustment before treatment and with good social support are more likely to benefit,^{14,15,21,39} but those with poorer psychosocial adjustment are important, from a public health and social order perspective, for methadone treatment and HIV infection and hepatitis prevention. In Ball and Ross's study, outcome was influenced negatively by age at first use of heroin, length of drug use, use of cocaine before treatment, and race, but these patient characteristics had less impact on outcome than did programme characteristics.¹²

PROGRAMME CHARACTERISTICS

Methadone maintenance programmes vary substantially in their effectiveness. In a study of six methadone clinics in the United States, ongoing use of injecting drugs varied from 10-25% in patients in the two most effective clinics to 56% in the least effective.¹² The more effective clinics were characterised by prescribing higher doses of methadone, having a treatment goal of successful ongoing maintenance rather than abstinence, and having better quality counselling, more medical services, better staff-patient relationships, low staff turnover rates, and better management.

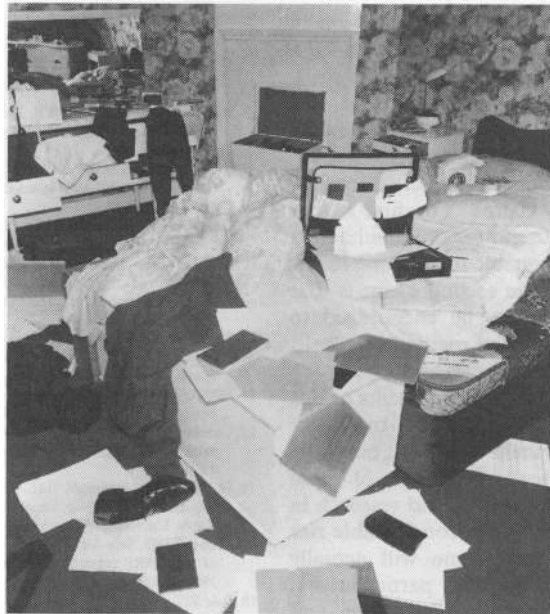
Dosage of prescribed methadone

A consistent relation is reported between higher doses of methadone (>50 mg), less illicit opioid use, and longer retention rates in treatment in randomised controlled trials⁴⁴⁻⁴⁶ and observational studies.^{12,21,39,47-50} Other studies have reported that lower doses of methadone have been associated with lower than average retention rates,⁵¹⁻⁵³ but some observational studies have reported otherwise.⁵⁴ One study in New York city reported that patients on lower doses of methadone were more likely to be HIV positive than those on higher doses.⁵⁵ These findings are especially pertinent to the United States, Australia, Britain, and much of the rest of Europe, where a model of treatment advocating low doses (20-40 mg) of methadone has been very influential.⁵⁶⁻⁵⁸

Daily doses that are appropriate in the longer term (as tolerance develops) may be fatal if instituted without care.^{40,41} A lethal dose for non-tolerant individuals is considered to be 70-75 mg.⁴² Careful assessment and careful induction should avoid such adverse outcomes,^{40,43} but even with the most careful induction process there have been reports of deaths of patients presumed to be opiate tolerant, owing to an idiosyncratic response probably reflecting differences in membrane stabilising potential among various opioids.⁵⁹ There is also evidence that a flexible dosage policy is associated with retaining patients in treatment.⁶⁰ Interpreting this research should therefore emphasise an appropriate therapeutic window for dosage of methadone (50-120 mg per day) as well as tailoring treatment according to individual need.

Maintenance versus abstinence

Several reports suggest that abstinence from all drugs, including methadone, may not be an appropriate treatment goal for many patients. Ball and Ross found that the most successful clinics had successful maintenance on methadone rather than abstinence as their goal of treatment.¹² Longer stays in treatment are associated with better outcomes overall,^{12,14,15,19-24} and the reason for ending treatment is highly predictive of subsequent functioning, with patients who end treatment with staff approval doing much better than those who leave for other reasons.^{15,19,20,24,61-63} When the time of methadone maintenance is limited in the



Crime is reduced—though not eliminated—when offenders are given methadone treatment for their drug habit

hope of increasing rehabilitation rates or cutting costs the outcome after treatment is poor.⁶⁴⁻⁶⁶ Studies that examined the fate of patients once they left treatment suggest that relapse rates are extremely high (70%).^{12 19 62 67} As well as those who complete treatment, the few patients who tend to do well after leaving methadone maintenance are those with shorter histories of opioid use and crime.¹⁹

Support services

The amount and quality of counselling and other social services are associated with treatment outcome,^{12 39 68-70} and two studies have reported a similar relation for medical services.^{12 39} The effectiveness of low intervention methadone maintenance (that is, the provision of methadone without supportive services) is currently an issue of debate.^{71 72} This form of methadone maintenance is probably quite common in many countries (Britain and Australia, for example) but has been formally evaluated only in the trial conducted recently in New York by Yancovitz *et al*.⁷¹ This study suggests that the provision of an adequate dose of methadone (60 mg) is sufficient to achieve reductions in heroin use, but the study period was very brief (one month) and further research is needed to establish the effectiveness or otherwise of providing methadone alone. More recently, McLellan *et al* have found a dose-response relation with increased support services for patients in methadone programmes, with better outcomes being achieved with better services.⁷⁰ The type and amount of services that should be made available to methadone recipients and which patients respond best to which type of treatment are important areas for research.

No studies have yet compared the performance of on site versus pharmacy based dispensing. Primary care or other individual practitioner approaches using community based dispensing facilities (as in the United Kingdom) have not been evaluated apart from a recently published descriptive retrospective case note study of methadone maintenance in general practice in Glasgow. This study reports high retention rates and high levels of reduction in illicit use and reduction in injecting comparable to optimal methadone programmes.⁷³ The costs seem comparable to those of specialised programmes. The overall resistance of general practitioners to substitute prescribing, and to maintenance prescribing in particular,^{74 75} will limit the involvement of general practitioners in this treatment.

Operational issues concerning methadone programmes

MONITORING USE OF NON-PRESCRIBED DRUGS

Urine analysis provides independent information on recent drug use. Clinical and cost considerations limit the frequency of monitoring. Important information can be obtained for individual assessment, for assessing programme performance, and for research purposes with urine analysis,⁷⁶ but the use that such information can be put to in modifying drug misuse is limited. Current evidence suggests that withdrawal of privileges, such as permission to collect a number of days' methadone supply at a time, on the basis of results of urine analysis is unlikely to have overall beneficial impact and may lead to less than acceptable retention rates.⁷⁷⁻⁸⁰ However, urine analysis results that indicate stability, with no use of non-prescribed or illicit drugs, can be used by the counsellor to build on progress.⁷⁹

DIVERSION OF METHADONE

The non-consumption and sale of methadone to unauthorised people has been a key force regulating the mode of prescribing and dispensing methadone in many countries. Despite this concern there is little evidence of the size of the problem of diversion or the impact of national regulations on such diversion. Anecdotal impressions suggest that the least regulated market, such as the United Kingdom, might have substantial diversion. The increasing numbers of notifications to the Home Office's addicts index of methadone dependence may be contributed to by methadone diversion. A major question is whether diversion results in doses that are less than effective.

Methadone related overdoses in children have been reported over two decades but have received little attention in Britain. Binchy and Molyneux reported on 44 accidental methadone overdoses with two deaths among children in Merseyside.⁸⁰ Such fatalities are a timely reminder of the dangers of methadone in the drug naive subject and the need for careful safekeeping of these drugs. Similarly, recent reports of deaths from the recreational use of methadone by drug naive subjects highlight the changes in unsupervised or unauthorised methadone consumption.

USE OF OTHER PSYCHOACTIVE DRUGS

Many people who use drugs heavily use a wide variety of substances. The use of other drugs, both licit and illicit, within methadone treatment programmes is a particular challenge to staff and programme delivery. The use of injectable cocaine is an important independent risk factor for the acquisition of HIV.^{28 31 82 83} Some studies have reported that risky injecting and syringe sharing behaviours increase with the use of multiple drugs^{35 84 85} and benzodiazepines.⁸⁵⁻⁸⁷ It is increasingly recognised that stabilisation of one pattern of drug misuse may be associated with ongoing problematic use of other substances. This indicates the importance of treatment interventions focusing on actual risk behaviour rather than simple categories of type of drug used. The substances most commonly misused are tobacco and alcohol, and patients may register high levels of physical morbidity related to alcohol and tobacco consumption. Continued interventions and monitoring of alcohol and tobacco consumption are important but often neglected dimensions of treatment.⁸⁸ The aggravation of cocaine and benzodiazepine related problems in the context of methadone treatment programmes requires further study.

ORAL OR INJECTABLE METHADONE?

Most of the international literature on methadone maintenance has been on the use of oral methadone. In

the United Kingdom there is widespread variation in the formulation of methadone prescribed, with high levels of prescribing of injectable methadone in some localities. Concerns have been expressed that this treatment modality may interfere with the benefits which some individuals may have otherwise accrued.

The rationale for the prescribing of injectable methadone is based on two claims. The first is that drug misusers who will not attend for oral methadone maintenance will attend if injectable methadone maintenance is made available.⁸⁹ The second claim is that such people will then be able to be encouraged to change over from injectable to oral methadone.^{90 91} In such cases injectable methadone serves as a gateway to oral maintenance. However, preliminary results of this approach show a disappointingly static treatment population with some movement towards, but little movement through, this gateway.⁹² Neither of these claims has been properly investigated, and research in this area is badly needed. There is a considerable risk that prescribing injectable methadone will actually increase the frequency of injecting, particularly if cocaine is also being injected with the methadone, and thereby have a net negative impact on risk reduction.

The alternative option of a longer acting oral form of methadone has been the subject of renewed interest in North America and Europe. The longer acting levomethadyl acetate may reduce frequency of dispensing to three times weekly but is unlikely to ameliorate the time required to have an impact on the complex psychosocial problems of many who attend methadone clinics. Levomethadyl acetate may provide interesting opportunities to compare some of the modalities of the treatment process.⁹³

Conclusion

Two authoritative bodies have reported on the benefits of methadone maintenance.^{3 38} The most recent report of the Advisory Council on Misuse of Drugs concludes that "The benefit to be gained from oral methadone maintenance programmes both in terms of individual and public health and cost effectiveness has now been clearly demonstrated and we conclude that the development of structured programmes in the UK would represent a major improvement in this area of service delivery." There is clear evidence that programmes may vary substantially in their efficacy.^{12 90}

Studies are required that will provide a clearer guide to the importance of treatment or programme structure and will define the minimum conditions necessary to deliver an effective intervention. Treatments such as methadone maintenance are costly, particularly because of the duration of treatment, but they are still substantially cheaper than the cost to the community of the active or incarcerated drug misuser. International reports find that oral methadone maintenance is justifiable on a cost-benefit analysis.³⁸ The challenge for researchers and planners is to define clearly the most cost effective method to deliver long term methadone treatment that has an appreciable impact on HIV infection, hepatitis, and other related risk behaviours, as well as improving social wellbeing for the individual and for the community.

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ANY QUESTIONS

Might the increase in the number of vaccinations in the past 20 years be a factor in the increased prevalence of asthma in children?

Many explanations have been put forward to account for the increasing prevalence of asthma, with studies suggesting that increased allergen load and perhaps increased levels of indoor and outdoor pollution are important. It is true that vaccination rates have increased in the past 20 years, and immunomodulation after vaccination could theoretically be the basis for some of the increase observed. No studies have yet addressed this possibility, and so the answer to this question must be speculative and based on the few studies that have looked at the influence of early viral infection on the development of asthma.

Viral infections are known to precipitate attacks of asthma in children, and raised levels of IgE follow a wide range of viral infections such as cytomegalovirus, Epstein-Barr virus infection, and influenza; influenza vaccine has similar effects on the immune system, also promoting the formation of IgE. Frick *et al* studied children at high risk of allergy because both parents were atopic.¹ Thirteen children were studied at three month intervals for two years and then six monthly up to four years. Eleven of the children became atopic, with positive results of radio-allergosorbent tests, antigen induced basophil histamine release, and raised IgE. In all these children upper respiratory tract viral infections had occurred one to two

months before sensitisation. One explanation would be that infection with virus (and thus possibly vaccination with modified viruses) leads to the development of allergy in susceptible subjects, but the converse could also be true: development of allergy may make children more susceptible to viral infection or exaggerate their symptoms so that they are recalled more easily on questioning.

A recent study has shown an inverse relation between the number of older siblings and the likelihood of allergic sensitisation.² It is suggested that early exposure to the viral infections of older siblings protects a child against the development of allergy. A similar explanation has been proposed to account for the low incidence of atopy in the former East Germany, where widespread provision of nursery facilities exposes children to viral infections in their early years. In the light of this, early vaccination could have two possible effects. It could provoke the same immunological response as viral infection, thus reducing the incidence of atopy. Alternatively, by protecting against childhood viral infections it might reduce the protective effect that these infections may have on the development of atopy and so lead to an increase in its incidence.—JONATHAN CORNE, *Medical Research Council training fellow, University of Southampton*

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