Justifying drug substitution therapies: The case of methadone maintenance treatment

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Introduction

Some time ago, I was told the story of a meeting that took place in a local community, the purpose of which was to decide whether a methadone clinic should be established there. At this meeting, members of the relevant government health authority and medical practitioners wanting to establish the clinic tried to alleviate community concerns about the clinic by talking about the evidence in favour of methadone maintenance and responding to concerns raised during the meeting. Concerns were raised about the possibility of the clinic attracting more heroin users to the area, the effects on local business, the risks associated with discarded needle and syringes, and so on. After long discussion, it appeared that the majority of the audience were convinced that methadone maintenance was an effective treatment for heroin dependence and their fears were assuaged by the arguments that they had heard. Just as the meeting was drawing to a close, one member of the audience raised her hand and wanted to know if methadone was a drug just like heroin. When it was answered, somewhat reluctantly by my informant that, yes, methadone was a drug that acted in ways similar to heroin, the mood of the meeting immediately changed, and, within a short period of time, it became clear that if methadone was a drug just like heroin, then people didn't want a methadone clinic in their community. What is more, they couldn't see how giving people a drug that was just like heroin that they would then be dependent on would be of any benefit anyway.

This story brings into focus the sometimes very different perspectives of those involved in drug treatment and policy formation and members of the concerned community. In many countries around the world the recent focus of academics, clinicians and policy makers has been on reducing the harms associated with the use of psychoactive drugs and not necessarily on eliminating the drug use or dependence itself (although it does not preclude this goal). Those who are opposed to the harm reduction approach see the drug use as the major harm and expect that treatments be focussed on abstinence from all drugs, including, in the case of heroin dependence, methadone. From this perspective, methadone maintenance is often said to simply substitute one drug for another.

Despite having been implemented and evaluated for nearly 40 years, methadone maintenance remains a controversial treatment. It is important then to be clear about what the rationale for methadone maintenance is and to evaluate the treatment in these terms, in the light of the accumulated research literature. However, I will argue that it is also important to examine the viability of the position of the critics of methadone maintenance treatment in the light of the relevant literature on opioid dependence, methadone maintenance treatment and the alternative treatments for heroin dependence, such as detoxification and drug-free residential treatment.

In considering these questions, I will argue that the appropriate comparison condition to the outcomes achieved by methadone maintenance and these other treatments is what would happen in the absence of treatment (Gerstein & Harwood, 1990) not some ideal state wherein all the individuals currently dependent on heroin would suddenly cease heroin use (Hall, 1993).

There have historically been two major rationales put forward for methadone maintenance treatment. The first was put forward by Dole and Nyswander (1965), who argued, on the model of diabetes mellitus, that long term exposure to an opioid, such as heroin, results in a "metabolic deficiency" that requires long term administration of a substitution opioid to manage it. The second, and more widely accepted, rationale for methadone maintenance treatment arose in the 1980s, after the widespread proliferation of and alarm about heroin use in many Western countries. This rationale is usually, but not always, associated with a harm reduction approach to the management of drug problems. According to this point of view, methadone maintenance is justified because the benefits that accrue from the treatment outweigh the risks associated with it for both the recipient of treatment and the community.

In the sections that follow, I will review evidence and arguments pertinent to an evaluation of the criticisms and justifications for methadone maintenance treatment. In doing so, I will begin by outlining the major features of opioid dependence and the harms associated with it. Then, after a brief history of methadone maintenance treatment, I will evaluate the criticism that it *simply* replaces dependence on one drug with dependence on another. The bulk of the remainder of the paper evaluates the evidence concerning the risks and benefits of methadone maintenance treatment, including a consideration of the most effective model of treatment delivery. In doing so, I will establish that methadone maintenance treatment is an effective treatment for heroin dependence in that it reduces heroin use, crime, HIV infection, and mortality. However, it is not a panacea for resolving all of the problems associated with heroin use. It does not prevent the spread of hepatitis C, and it does not lead to improvement in all individuals who present for treatment, although it does lead to improvement in the majority of those who present.

Opioid dependence

The most commonly used illicit opioid in most countries around the world is heroin. Of those who use this drug, approximately one-quarter develop dependence (Anthony & Helzer, 1995). After becoming dependent, a typical picture emerges of daily heroin-use, interrupted by periods of detoxification and imprisonment, but with most individuals returning soon after to daily use. This use is continued despite a range of serious legal, health, financial and interpersonal problems that are typically associated with daily heroin use.

Most heroin dependent individuals present for treatment as result of pressure from family and friends, or because they have been arrested for a drug-related offence (Gerstein & Harwood, 1990). In the short term, only a small proportion achieve abstinence as a result of treatment. Over a 20 year period, about one-third of those who enter treatment and are then followed will achieve abstinence, which is approximately the same proportion as those who will die in the same period (Goldstein & Hen-era, 1995; Hser, Anglin, & Powers, 1993). The remaining third who continue to use heroin cycle through prisons, treatment programs and daily heroin use well into their 40s and 50s. When not in prison or attending a treatment program, these people use heroin on a daily basis about 40-60% of the time (Maddux & Desmond, 1992).

Illicit heroin use is associated with a range of health and social problems for both the community and the user. People who use heroin are at increased risk of death from overdose, violence, viral infections and alcohol-related morbidity (alcohol dependence being a common comorbid condition in this population; Goldstein & Herrera, 1995; Haastrup & Jepsen, 1984; Hser et al., 1993; Joe & Simpson, 1987;

Perucci, Davoli, Rapiti, Abeni, & Forastiere, 1991; Perucci, Forastiere, Rapiti, Davoli, *&*. Abeni, 1992). While tobacco and alcohol are the major causes of drug-related morbidity and mortality, among young adults, opioids are most prominent as causing drug-related deaths. In Australia, for example, death by opioid overdose is a major cause of death among young adults (Laslett & Rumbold, 1998), Death from overdose and injection-related viral infections is less likely among individuals who ingest heroin intranasaliy or by smoking than among those who inject it. Among those who do inject, heroin users act as an important host population for hepatitis B and C and HIV (Crofts, Thompson, & Kaldor, 1999). People who use heroin are also responsible for a significant proportion of criminal offences, which they commit in order to support the purchase of heroin (Hall, Bell, & Carless, 1993).

Methadone and Methadone Maintenance Treatment

Methadone is a synthetic opioid substance that has effects in human beings similar to heroin. However, unlike heroin, methadone is easily absorbed from the gut and so can be taken orally, whereas heroin is usually injected. Once absorbed via the gut, methadone has a relatively long elimination half-life (approximately 24-36 hours), making it particularly suitable for managing withdrawal from heroin, which has a much shorter elimination half-life (3-6 hours). As early as 1949, research conducted in the United States identified methadone as a useful agent for detoxifying people addicted to heroin (Joseph, Stancliff, & Langrod, 2000). However, it wasn't until 1964, that Vincent Dole and Marie Nyswander conducted clinical research in New York City to identify a suitable replacement for heroin that methadone was used for longer term treatment (Courtwright, Joseph, & Des Jarlais, 1989; Joseph et al., 2000).

After trying various opioid substances as heroin substitutes, Dole and Nyswander discovered that the most clinically useful drug that suited the purposes of a maintenance treatment program was methadone. The long elimination half-life meant that patients could be dispensed methadone once a day, compared with several times a day in the case of drugs such as morphine and heroin. The oral mode of administration had a number of attractive features associated with it. It obviated the need for injection, but more importantly, it meant that the rapid intoxication experienced after the injection of heroin could be avoided, because when taken orally, methadone is absorbed slowly into the bloodstream. Furthermore, once the person was stabilised on methadone, they appeared not to experience any significant intoxication, Once the successful results of an early series of cases was published (Dole & Nyswander, 1965), followed by further reports of treatment success (Dole, Nyswander, & Wamer, 1968; Dole et al., 1969), methadone maintenance treatment was adopted widely in the United States and was soon established in other countries, such as Australia and the United Kingdom (Zador, 2001; Caplehom & Batey, 1992). However, this initial enthusiasm was soon tempered by criticisms of the treatment that it medicated the disaffected and simply substituted one drug for another (e.g. Nelkin, 1973).

In their rationale for methadone maintenance treatment Dole and Nyswander viewed opioid dependence as ‘a physiological disease characterised by a permanent metabolic deficiency’ which was best treated by administering ‘a sufficient amount of drug to stabilise the metabolic deficiency’ (Dole & Nyswander, 1965). Stabilisation was achieved by providing high or ‘blockade’ daily doses of oral methadone, which prevented withdrawal symptoms, removed the craving for heroin, and blocked its euphoric effects if the person injected heroin. While patients were maintained on methadone, they could also take advantage of the rehabilitative services that were an integral part of the program (Dole & Nyswander, 1967). The key features of the Dole and Nyswander formulation then were long-term treatment, high doses of methadone and a comprehensive set of psychological and social services to assist the person to reintegrate into mainstream society.

In the process of the popularisation of methadone maintenance in the United States, the treatment underwent a number of important changes that compromised its effectiveness (Gerstein & Harwood, 1990). Most of these changes were made in response to the criticisms of the Dole and Nyswander metabolic deficiency hypothesis which was widely thought to be implausible. As a result, the treatment goal of many programs shifted from long-term maintenance towards achieving abstinence from all opioid drugs, including methadone, within a period of a few years. The average dose of methadone also declined from the high doses favoured by Dole and Nyswander to the much lower doses that were required to simply avert withdrawal symptoms. Furthermore, as a result of funding cuts, the extent of ancillary services declined.

More recently, national surveys of treatment practices in the United States (D'Aunno & Vaughn, 1992; General Accounting Office, 1990) and literature reviews pertinent to the way methadone treatment is delivered have recommended changes in treatment practice to bring it back in fine with the original Dole and Nyswander formulation (Gerstein & Harwood, 1990; Institute of Medicine, 1995; Ward, Mattick, & Hall, 1992). Recent evidence suggests that there is a return to the original Dole and Nyswander formulation, in using higher methadone doses and having an orientation toward long- rather than short-term treatment (D'Aunno, Folz-Murphy, & Lin, 1999). The evidence concerning the effectiveness of intensive psychosocial services remains mixed and debate continues on this issue.

While many countries adopted a model of methadone maintenance treatment that was based on daily attendance at a specialist clinic with supervised ingestion of methadone, in the United Kingdom, a different model developed which involved prescribing by generalist medical practitioners and pharmacy dispensing of both injectable and oral methadone (Zador, 2001). Recent controlled trials in the United States of a similar model developed in the United States support the effectiveness of this model of methadone treatment, at least for patients who are responding well to treatment (Fiellin et al., 2001; King et al., 2002).

Controversies About Methadone Maintenance

Despite the evidence attesting to its effectiveness, there are critics who have strong moral reservations about methadone maintenance treatment. These moral reservations are concerned with whether it is justifiable to dispense a drug of dependence to drug dependent individuals, especially within the Dole and Nyswander model of long-term maintenance. However, while there are still a few who subscribe to the original Dole and Nyswander conceptualisation of opioid dependence as a metabolic disease (but restated as a long term opioid receptor perturbation; e.g. Dole, 1988; Kreek, 1996), the more usual contemporary justification is a pragmatic utilitarian one – methadone maintenance is justified because the benefits far outweigh the risks associated with it.

While accepting Hume's argument that statements about what one ought to do cannot be inferred from statements about what is the case. Hall, Ward and Mattick (1998) nonetheless argue that empirical evidence is relevant to the evaluation of moral principles, as do many modem ethicists (eg. Rachels, 1986). If we begin with the pragmatic utilitarian justification for methadone maintenance treatment, the role of empirical evidence is very clear. Methadone maintenance treatment is justified, on utilitarian moral grounds, if the benefits of the treatment to both the patients and the community outweigh its costs. It is then important to demonstrate that methadone maintenance treatment reduces the harms associated with dependent heroin use without incurring greater harms to its recipients and the community.

Some opponents of methadone maintenance argue that methadone maintenance treatment fails to achieve these goals in that substantial numbers of methadone patients continue to inject illicit drugs and engage in criminal activity. Research evidence on the outcome of methadone maintenance is clearly relevant to an evaluation of these competing claims.

However, an appraisal of the costs and benefits associated with methadone maintenance treatment does not address the key objection that methadone maintenance is unacceptable because it simply 'replaces one drug of dependence with another'. According to this point of view the only viable outcome from any treatment for opioid dependence is abstinence from all opioid drugs, including methadone. Hall et al. (1998) argue that empirical evidence is also relevant to an evaluation of this moral objection for the reason outlined by Kant in the late eighteenth century. If it can be shown that a moral obligation is empirically impossible, or at least extremely difficult to meet, there is a good reason to modify it. The moral claim that abstinence is the only acceptable outcome for treatments for opioid dependence depends upon the assumption that abstinence is an attainable state for a majority of opioid dependent people. There is a considerable body of research evidence that contradicts this assumption. This research includes the studies reporting the outcome of opioid detoxification and drug-free treatment, and a small number of studies of the 'natural history' of opioid dependence (e.g. Gerstein & Harwood, 1990; Stimson & Oppenheimer, 1982; Thorley, 1980; Vaillant, 1966, 1973). These studies clearly show that the majority of participants relapse to heroin use shortly after detoxification.

A related criticism of methadone maintenance treatment is that it prolongs opioid dependence by maintaining people on methadone when they otherwise would become drug free. It was this criticism that led to a shortening of the duration of treatment during the 1970s and 1980s. Again empirical evidence is relevant to this claim. Long-term follow-up studies have found equivalent rates of abstinence among untreated individuals and individuals who have been in methadone maintenance treatment (Goldstein & Herrera, 1995; Hser et al., 1993). The same is true for people who enter methadone maintenance treatment and drug free treatment (Maddux & Desmond, 1992). This evidence suggests that methadone maintenance does not prolong opioid dependence or impede eventual abstinence.

The difficulty of achieving abstinence does not preclude abstinence as a viable treatment goal for opioid-dependent people. Drug-free treatments, which aim to achieve abstinence, clearly have a place in the treatment response for those opioid-dependent people who want to become abstinent and find this form of treatment acceptable.

However, it is clear from the high failure rate of abstinence-oriented programs that there is no compelling moral reason for insisting that abstinence from all opioids is the *only* acceptable treatment goal for those who are opioid dependent, especially in the case of those who have tried and failed to achieve abstinence. To insist on such a goal is to condemn those dependent on heroin to a high risk of death, imprisonment and chronic disease.

THE BENEFITS OF METHADONE MAINTENANCE TREATMENT

In the sections that follow, I will review the evidence concerning the effectiveness of methadone maintenance treatment with reference to the major harms associated with opioid dependence. In doing so, I will evaluate the claim put forward as part of the utilitarian justification for methadone maintenance treatment; that it reduces heroin use and thereby the morbidity and mortality associated with its use. Given the large number of studies that have been published, this review will necessarily be brief, and so I will focus in detail on recent and indicative studies. A more detailed coverage of this literature can be found in Ward, Mattick and Hall (1998e).

Heroin Use And Crime

There have been seven randomised controlled trials in which methadone maintenance has been compared with a non-drug substitution control group for either part or all of the study period (Dole et al., 1969; Gunne & Gronbladh, 1981; Newman & Whitehill, 1979; Sees et al., 2000; Strain, Stitzer, Liebson, & Bigelow, 1993; Vanichseni, Wongsuwan, Staff of the BMA Narcotics Clinic No. 6, Choopanya, & Wongpanich, 1991; Yancovitz et al., 1991). Methadone maintenance has also been used as a comparison treatment in trials investigating the effectiveness of other pharmacotherapies such as buprenorphine (Mattick, Oliphant, Ward, & Hall, 1998), but these trials do not bear directly on the assessment of the effectiveness of methadone maintenance treatment and will not be discussed further here.

All of the randomised controlled trials have found significant effects in favour of the provision of methadone in terms of reductions in heroin use and/or crime. The three earliest trials (Dole et al., 1969; Gunne & Gronbladh, 1981; Newman & Whitehill, 1979) together indicate that methadone maintenance retained patients in treatment and led to large reductions in heroin use and likelihood of reimprisonment, when compared with untreated controls. The trial reported by Strain et al. (1993) found methadone maintenance led to less heroin and cocaine use than a placebo treatment. The trials by Vanichseni et al. (1991) and Yancovitz et al. (1991) have found smaller effects and have followed participating subjects for only short study periods.

These smaller effect sizes are consistent with the findings of a meta-analysis recently published by Prendergast, Podus and Chang (2000), who reported that the size of the effect in studies of methadone maintenance treatment has diminished over the past three decades. Likely reasons for this diminishing effect size are less than adequate implementation of the treatment and changes in the drug use patterns of the patients being treated.

In a study that bears on a number of questions raised in this paper. Sees et al. (2000) compared 180-day methadone-assisted detoxification with compulsory intensive psychosocial services and aftercare with standard methadone maintenance treatment. The study provides evidence pertinent to answering questions about the effectiveness of methadone maintenance treatment, about how long it should be provided for and about the role of intensive psychosocial services in its effectiveness.

The question that Sees et al. set out to answer was whether, over a 12-month period, equivalent outcomes to methadone maintenance could be achieved in terms of drug use, HIV risk behaviour and psychosocial functioning by offering a 6-month methadone detoxification program that included intensive psychosocial services and aftercare for the subsequent 6 months. After being stratified by sex and ethnicity, participants in the study were randomly assigned to receive either long-term methadone detoxification (n=88) or methadone maintenance (n=91). Both groups were stabilised on an average of approximately 85mg per day of methadone. After four months of maintenance the methadone detoxification group was detoxified in a gradual fashion over the subsequent two months. Participants in the detoxification program were required to attend weekly individual and group psychotherapy and education sessions. If there was evidence of cocaine use, they were also required to attend a weekly therapy group for cocaine users. By contrast, in the methadone maintenance group, participants were required to attend a weekly group for the first six months, after which attendance was voluntary. They also attended for monthly individual therapy for the duration of the study. Aftercare for the detoxification group consisted of continued therapy and assistance with criminal, medical and social service referrals. All participants were assessed at baseline and then monthly for the 12 months of the study on all the study outcomes and on their exposure to treatment components received in the previous month from both study and non-study treatment programs.

The analysis of the data for this study was done an intention-to-treat basis. The first finding of interest was that retention between the two groups was different with the detoxification group dropping out of treatment more quickly than the methadone group.

While approximately 70% of the methadone maintenance group remained in treatment after one year, most of the members of the detoxification group left treatment once methadone provision began to be tapered. This shows, as did the Newman and Whitehill (1979) and Strain et al. (1993) placebo-controlled trials that methadone is an essential part of a methadone maintenance program and that intensive services are not attractive when it is absent.

Heroin use was analyzed in terms of whether there was any evidence of heroin use in the previous month as measured by urine test or self-report and in terms of the number of days of heroin use reported for the previous month. Both of these analyses revealed that there were no differences between the two groups for the first four months of the study, but once methadone reduction began in the detoxification group differences emerged and persisted throughout the subsequent follow-up period. These findings for heroin use, were confirmed by the findings for HIV risk behaviour. Again there were differences between the two groups in injection-related risk behaviour once detoxification had taken place.

Overall the study by Sees et al. suggests that methadone maintenance treatment is more effective than methadone detoxification after four months maintenance and that the provision of intensive psychosocial services is not sufficient to replace the daily administration of methadone. The authors of the paper concluded that: “the current study does not provide support for diverting resources from methadone maintenance to long-term detoxification, no matter how ideologically attractive the notion of a time limited treatment for opioid abusers is.” (p. 1309)

These findings from randomised controlled trials are supported by a much larger body of cohort and cross sectional studies (e.g. Anglin & McGlothlin, 1984; Bale et al., 1980; Ball & Ross, 1991; Gossop, Marsden, Stewart, & Roife, 2000; Hubbard, Craddock, Flynn, Anderson, & Etheridge, 1997; Hubbard et al., 1989; Simpson & Sells, 1982). The observational studies of the effectiveness of methadone maintenance treatment support the results of the randomised controlled trials in consistently showing that methadone maintenance reduces heroin use and criminal activity.

HIV

As well as reducing heroin use and crime, an important area in which methadone maintenance treatment is expected to be effective is in the reduction of HIV infection among heroin users. More recently, concern has also been raised about the spread of hepatitis C in this population. HIV and HCV are the two viruses most often transmitted among injecting drug users as a result of sharing injecting equipment (Hagan & Des Jarlais, 2000). The evidence pertaining to HCV is reviewed in the next section below.

There are two kinds of evidence relevant to a consideration of the role of methadone maintenance programs in reducing the spread of HIV: studies that directly evaluate the protective effect of methadone treatment in terms of HIV seroprevalence rates, and studies that examine whether methadone maintenance treatment reduces those drug use behaviours implicated in the spread of HIV among injecting drug users. Recent reviews have consistently concluded that methadone maintenance treatment is effective in reducing the spread of HIV and in reducing the injection-related behaviours known to transmit it (Marsch, 1998; Sorensen & Copeland, 2000; Ward, Mattick, & Hall, 1998a). The studies reviewed here are indicative of the much larger body of evidence surveyed in these reviews.

Initial evidence for the effectiveness of methadone maintenance in preventing HIV infection came from retrospective studies that found an association between length of time in methadone treatment and low rates ofseropositivity (Abdul-Quader et al., 1987;Chaissonetai., 1989; Manner et al., 1987; Novicket al., 1990; Schoenbaum et al., 1989). These findings were confirmed by prospective studies that showed that entry to methadone maintenance treatment led to reduced rates of HIV infection compared with individuals who either did not enter, or who left treatment (Blix & Gronbladh, 1988; Des Jarlais, 1992; Institute of Medicine, 1995; Metzger et al., 1993; Moss et al., 1994; Serpelloni et al., 1994). Other evidence suggests that these findings can be attributed to the fact that patients who remain in methadone maintenance are less likely to engage in risk behaviours compared with those who leave methadone treatment early or do not enter treatment at all (Ball & Ross, 1991; Brown, Chu, Nemoto, Ajuiuchukwu, & Primm, 1989; Caplehom & Ross, 1995; Darke, Hall, & Carless, 1990; Klee, Faugier, Hayes, & Morris, 1991; Longshore, Hsieh, Danila, & Anglin, 1993; Selwyn, Feiner, Cox, Lipshutz, & Cohen, 1987; Stark & Muller, 1993). Both these lines of evidence are important in concluding that methadone maintenance treatment prevents to the spread of HIV in populations of heroin injectors.

Hepatitis C

While the published evidence supports the conclusion that methadone maintenance treatment is effective in reducing HIV infection among heroin users, the evidence is less sanguine in relation to the hepatitis C virus (HCV). In recent years, it has been discovered that HCV has been a "sleeping" health issue for injecting drug users (Novick, 2000) for some time. However, the transmission dynamics of HIV and HCV are different, with HCV being more readily transmitted than HIV (Crofts et al., 1999; Hagan & Des Jarlais, 2000), and so conclusions drawn from studies of methadone maintenance and HIV cannot be generalised to HCV. To date, studies examining the effectiveness of methadone maintenance in preventing infection with HCV have found no such effect (Crofts, Nigro, OMan, Stevenson, & Sherman. 1997).

This is not surprising given the high rates of infection seen at intake to treatment. For those not yet infected, as Novick (2000) has observed, even occasional injection drug use can cause HCV infection, because of the high likelihood of transmission of HCV, This means that methadone maintenance is unlikely to protect the substantial proportion of patients who continue to use heroin at least sporadically.

Drug-related Mortality

As already noted, opioid dependence is associated with a high risk of mortality, and, as a result, mortality is an important outcome to consider in evaluating the effectiveness of methadone maintenance. Common causes of death among the opioid dependent are drug overdose, cirrhosis, endocarditis, violence, AIDS-related illnesses and, more recently, HCV-related liver disease (Appel, Joseph, & Richman, 2000; Haastrup & Jepsen, 1984; User et al., 1993; Joe & Simpson, 1987). Compared to untreated opioid dependent individuals, those receiving methadone maintenance have a reduced risk of dying (Appel et al., 2000; Caplehom, Dalton, Cluff, & Petrenas, 1994; Davoli et al., 1993; Desmond & Maddux, 2000; Gearing & Schweitzer, 1974; Gronbladh, Ohiund, & Gunne, 1990). For example, Gronbladh et al. (1990), in a six year follow-up of individuals who participated in the Swedish randomised controlled trial (Gunne & Gronbladh, 1981), reported that untreated controls had a death rate 73 times that expected for their age group, while none of the subjects who had received methadone treatment had died. In a case-control study of overdose deaths among 4200 methadone clients in Rome during the period 1980-1988, Davoli and colleagues (1993) found that individuals who left treatment were eight times more likely to die during the year after they left compared with clients who stayed.

More recently, Appel et al. (2000) reported the results of a study of mortality during and after methadone treatment for a cohort of patients described by Dole and Joseph (1978). The sample consisted of 1,544 patients admitted to methadone maintenance in two cohorts, one in 1966-1967 and the other in 1972. The study conducted in 1981 examined causes of death and death rates for the ten-year period 1966-1976. During this time, there were 176 deaths among the 1544 patients. Of these 93 deaths occurred during methadone maintenance and 83 after methadone maintenance. Ignoring cause of death, the post-treatment death rate among the former patients was double that of those receiving methadone maintenance treatment. When these deaths were examined according to cause of death, it was found that only 2 opiate-related deaths occurred during treatment, while 36 occurred out of treatment. This represented a 51 times greater risk of dying from opiate-related causes after leaving methadone maintenance (15.3 deaths per 1000 years), when compared with those remaining in treatment (0.3 deaths per 1000 years).

As Desmond and Maddux (2000) have recently observed in a review of this literature, these

studies have been conducted in four different countries by different researchers. and so we can be more confident in concluding that methadone maintenance reduces the high risk of mortality associated with heroin use. As Desmond and Maddux further note, this effect is mainly restricted to mortality due to heroin overdose, a conclusion that is further supported by the findings reported by Appeal in the same year. Finally van Ameijden, Langendam and Coutinho (1999) have recently reported finding a dose-response relationship between daily methadone dose and risk for mortality. Although lower doses (<55mg) were effective in reducing mortality, there was a threefold reduction in mortality for those on higher doses when compared to those on lower doses.

The benefits of methadone maintenance treatment: Conclusions

The findings of the review of the literature in the previous sections are that methadone maintenance treatment is effective in reducing heroin use, crime, drug-related mortality and HIV infection among heroin dependent individuals. However, it is not effective in reducing the spread ofHCV in this population. These conclusions are consistent with more extensive reviews conducted by my colleagues and I (Ward et al., 1992, 1998e) and with reviews conducted by other reviewers (Des Jarlais, 1994; Gerstein & Harwood, 1990; Marsch, 1998; Sorensen & Copeland, 2000). The review reported by Marsch is unique in that, unlike all the other reviews, which were qualitative in nature, a quantitative approach was taken using meta-analysis. Despite inclusion criteria restricting the selection of studies to those that employed fixed dosage schedules irrespective of patients' heroin use (a procedure makes little clinical sense), Marsch found that methadone maintenance treatment was successful in reducing heroin use, drug-related and to a lesser extent non drug-related crime, and HIV risk behaviour. The biggest effect found in the studies reviewed was for drug-related crime.

GETTING THE FORMULATION RIGHT

As I have noted above, observational studies of the effectiveness of methadone maintenance treatment suggest that some methadone clinics are more effective than others. The key variables that have been identified as being important in this variation are the three that were identified as being central to the Dole and Nyswander model of treatment – methadone dose, the duration of treatment and adjunctive psychosocial services.

In this section, I review the evidence concerning these treatment characteristics. I also review the evidence pertinent to a consideration of injectable versus oral methadone maintenance.

Methadone Dosage

The original formulation for methadone maintenance treatment, as devised by Dole and Nyswander (1965), included high doses of methadone. The use of high maintenance doses of methadone (>60 mg per day) was originally meant to achieve three purposes: to prevent withdrawal symptoms, to induce a sufficient cross-tolerance to heroin to prevent intoxication, and to prevent craving for heroin. However, in many clinics lower doses have been prescribed, and as Leavitt, Shinderman, Maxwell and Paris (2000) have recently remarked, this has more to do with philosophical, psychological and moral reasons than empirical evidence. The evidence, which consists of both randomised controlled trials and observational studies, clearly shows that higher doses of methadone lead to longer stays in treatment and less heroin use (e.g. Banys, Tusel, Sees, Reilly, & Delucchi, 1994; Caplehorn, Bell, Klein, & Gebski, 1993; Hartel et al., 1995; Maddux, Prihoda, & Vogtsberger, 1997; Magura, Nwakeze, & Demsky, 1998; Strain, Bigeiow, Liebson, & Stitzer, 1999; Strain et al., 1993). In a recent study, Preston, Umbricht and Epstein (2000) have found that increasing methadone dose in response to ongoing heroin use is as effective as paying patients not to use heroin. A more extensive review of this literature can be found in Ward, Mattick and Hall (1998d).

Duration of Treatment

There is substantial evidence that longer stays in methadone maintenance treatment are associated with better treatment outcomes in terms of less heroin use and crime (for recent reviews see Magura & Rosenblum, 2001; Prendergast et al., 2000; Ward, Mattick, & Hall, 1998b). However, the important question for this paper is whether varying the length of treatment, as originally formulated by Dole and Nyswander, improves or detracts from the effectiveness of methadone maintenance treatment. The evidence clearly suggests that arbitrarily restricting the length of treatment leads to poor post-treatment outcomes for most patients (Anglin, Speckart, Booth, & Ryan, 1989; McGlothlin & Anglin, 1981; Rosenbaum, Irwin, & Murphy, 1988). More light is shed on this issue when we consider the evidence concerning reasons for leaving treatment and post-treatment success. Some individuals leave treatment before they have shown the relevant prognostic indicators of post-treatment success, such as signs of psychosocial stabilization.

These individuals are more likely to return to regular heroin use than patients who do show such signs (Cushman, 1978; Simpson, 1981; Stimmel, Goldberg, Cohen, & Rotkopf, 1978). However, the accumulated evidence on this issue suggests that few patients show such signs and most who leave treatment do so when these signs suggest that it would be better for them to remain in treatment (Magura & Rosenblum, 2001). Considered as a whole then, this evidence suggests that methadone treatment with an orientation toward long term maintenance, as originally formulated by Dole and Nyswander, is the most appropriate orientation for the majority of patients who enter it.

Psychosocial Services

Given the well-documented high levels of medical, psychiatric and social problems found among opioid users (Darke, 1998; Ward, Mattick, & Hall, 1998c), there is an obvious case to argue that the provision of medical and psychosocial services in methadone maintenance programs is part of a thoughtful response to problems created by opioid use. Therefore, as well as providing methadone, it is also thought to be appropriate to provide treatment and assistance to address these factors. Such services were part of the original Dole and Nyswander formulation. While the rationale for such services seems reasonable, the question remains whether the effectiveness of methadone maintenance treatment is improved by providing a full range of ancillary services, such as medical treatment, addiction counseling, psychotherapy, and so on, or whether there is an optimal level of service provision. These services often comprise the most expensive components of a methadone treatment program, and so it is important to ask how much more effective treatment becomes when these services are provided and how much it costs to provide them.

There is evidence supporting the effectiveness of drug counseling (Ball & Ross, 1991; Magura, Nwakeze, Sung-Yeon, & Demsky, 1999; McLellan, Amdt, Metzger, Woody, & O'Brien, 1993; McLellan, Woody, Luborsky, & Goehl, 1988), psychotherapy for comorbid psychiatric problems (Woody, McLellan, Luborsky, & O'Brien, 1995; Woody et al., 1984), and primary health care services (Ball & Ross, 1991; McLellan et al., 1994; Umbricht-Schneiter, Ginn, Pabst, & Bigelow, 1994) in improving outcomes from methadone maintenance treatment. Another way in which this question has been examined has been to examine whether varying the intensity of ancillary services results in variations in the effectiveness of treatment. In one of the best studies designed to address this issue, McLellan et al, (1993) randomized 92 male war veterans to minimal, standard or enhanced methadone maintenance treatment and found increasing improvements in outcome across the three levels of service. In 1997, Krart, Rothbard, Hadley, McLellan and Asch (1997) examined the costs associated with the three levels of services in relation to the outcomes achieved. Kraft et al. concluded that there is a level of service provision, below which treatment becomes more, rather than less, expensive.

The results suggested that the provision of counseling services in addition to daily methadone is the most cost effective, with the provision of more elaborate services (psychotherapy, vocational counseling and so on) leading to only marginal improvements in outcome for much greater cost.

More recently, Avants et al. (1999) randomised 291 patients to receive, for 12 weeks, either a two-hour per week, cognitive behavioural therapy group, or a five hour per day, high intensive program of groups that addressed a range of issues, including drug use, health issues, and living and social skills. Outcome was assessed on a range of indicators measured by self-report using the Addiction Severity Index and, in the case of heroin and cocaine use, by urine test. Overall both groups showed improvement at the end of the 3-month study period and at 6-month follow-up after program completion, but there were no differences between the two groups at either time. The only differences were for those patients who were new to methadone maintenance and for them participation in the lower intensity program led to better retention and higher rates of abstinence at six-month follow-up. When asked prior to the study which program participants preferred, the majority (78%) nominated the low intensity program. This study guarded against the problem of patients not receiving the services delivered by ensuring compliance. However, as the authors note, participants in this study received these services regardless of whether they needed them or not, so the question of which services are appropriate for which patient was not addressed.

At this time, the evidence suggests that offering counseling and medical care improve outcomes from methadone maintenance treatment. However, providing high intensity programs with a range of other services does not seem to improve outcome over and above what is achievable with this level of service provision. Small improvements may be observed, but given the ever-increasing demand for treatment, resources may be better spent in providing more treatment places with lower levels of services than more intensive services for fewer patients.

INJECTABLE VERSUS ORAL METHADONE MAINTENANCE

Methadone can be dispensed as either an oral or an injectable preparation. Injectable methadone is prescribed routinely in the United Kingdom but is not available in most other countries, although this is changing (Zador, 2001). The main rationale for the provision of injectable methadone is that it will attract into treatment individuals who would not otherwise present for oral methadone. This assumption has yet to be tested empirically and given the added risks associated with injecting rather than orally ingesting methadone, it is worthy of investigation. However, assuming that injectable methadone maintenance is a viable alternative to an oral regimen, the question arises as to whether one mode of administration is more effective than the other.

Strang et al. (2000) recently published the findings of a randomised controlled trial in which 40 applicants for methadone treatment were assigned to receive supervised oral methadone or supervised injectable methadone. The practice of supervised injecting is unusual for the Uniled Kingdom, where methadone ampoules are usually dispensed at a pharmacy. This trial was prompted by the Swiss experience in running such facilities. Similar to the findings reported much earlier by Hartnoll et al. (1980), who compared oral methadone with injectable heroin in the United Kingdom, the study found no differences between the two groups in heroin or other drug use six months after treatment commenced. There were no differences in retention between the two groups. However, patients assigned to the supervised injectable condition reported being more satisfied with treatment than those assigned to the oral methadone group. Strang and colleagues also assessed the comparative cost of the medication and provision of services and found that the cost of the injectable methadone program was approximately 4 to 5 times higher than the oral methadone program. On the basis of the findings of this study we can conclude that injectable methadone is as effective as oral methadone and leads to greater patient satisfaction, but that the cost involved is much higher. Only longer term studies would be able to identify whether the increase in satisfaction translates into better retention rates.

RISKS ASSOCIATED WITH METHADONE MAINTENANCE TREATMENT

As has been shown in the previous sections, methadone maintenance treatment reduces heroin use, crime, overdose mortality and the spread of HIV. However, as with most other pharmacotherapies employed in modem medicine, there are risks associated with the prolonged use of methadone that have to be considered in arriving at definitive conclusions about the benefits of methadone maintenance. Nies (1990) summarises the nature of this evaluation as follows: “The utility of a regimen can be defined as the benefit it produces plus the dangers of not treating the disease minus the sum of the adverse effects of therapy”(p. 74). In this section, I consider the safety of the long-term administration of methadone, the risk of death associated with the induction phase of treatment and problems created by the diversion of methadone from those to whom it has been prescribed.

Safety of Long Term Methadone Administration

The main side effects of taking methadone on a daily basis are increased perspiration and constipation (Joseph et al., 2000). An investigation of the consequences of long-term methadone administration among a cohort of patients in New York City who had been in treatment for ten years or more found no adverse effects as a result of treatment (Novick et al., 1993).

However, it has to be acknowledge that ‘street lore’ about methadone maintains the view that it is associated with a range of ills that vary from non-specific aches and pains through to devitalising previously vital individuals (Bourgois, 2000; Hunt, Lipton, Goldsmith, Strug, & Spunt, 1985-86) and that this ethnographic literature contradicts in some ways the more objective medical literature.

Mortality During the Induction Phase of Treatment

The first two weeks of methadone treatment has been found to be a time when there is an increased risk of death due to methadone overdose (Humeniuk, Ali, White, Hall, & Farrelt, 2000). In Australia, most of these deaths are associated with the concomitant use of other central nervous system depressants. However, rapid escalation of; methadone dose during the first days of treatment is also implicated (Drummer, Opeskin, Syrjanen, & Cordner, 1992). These deaths are most readily avoided by the proper training of medical practitioners involved in methadone prescribing and by educating drug users about the safe use of methadone (Ali & Quigley, 1999).

Diversion of Methadone

Another risk of methadone maintenance treatment is the diversion of methadone to persons other than the patient in treatment. Methadone, especially if dispensed in a take-home manner, can be given away or sold to other people for their own use. The main risk associated with the use of diverted methadone is death by overdose. For example, an increase in the availability of methadone in Manchester led to a parallel increase in deaths attributed to diverted methadone (Caims, Roberts, & Benbow, 1996). Similar results have been reported from Germany (Heinemann, Iwersen-Bergmann, Stein, Schmotdt, & Piischel, 2000) and Switzerland (Perret, Deglon, Kreek, Ho, & Harpe, 2000). However, as Bell and Zador (2000) have observed this risk varies according to the extent to which take-home methadone is made available. For example, heroin use is the major cause of opioid-related death in Australia where take-home methadone is relatively restricted, whereas in the United Kingdom, which has a more liberal take-home dispensing policy, methadone accounts for about half the opioid related deaths (Bell & Zador, 2000). As Bell (2000) has observed, methadone programs that allow overly liberal take-away methadone will ultimately threaten methadone maintenance as a viable treatment modality. After considering this issue, the United States Institute of Medicine (1995) concluded that methadone diversion is a serious concern, but not one that would warrant restricting the availability of an effective treatment to those in need. Take-home methadone for stable patients is a necessary part of treatment for individuals who find it difficult to attend on a daily base for supervised dispensing (e.g. mothers of young children, employed patients, the chronically ill).

CONCLUSIONS

In this paper, I have reviewed the evidence pertinent to a consideration of the effectiveness of methadone maintenance treatment in the light of the moral justification for and the moral objections to this form of treatment. This evidence suggests that methadone maintenance treatment is effective in reducing heroin use, crime, drug-related mortality and HIV. However, it does not appear to be effective in the spread of HCV among injecting opioid users. In achieving these outcomes, methadone maintenance does not prolong dependence any longer than would occur in the absence of treatment or in cases where the person enters some other form of treatment. The formulation of methadone maintenance originally developed by Dole and Nyswander is supported by the available evidence. The evidence clearly supports the provision of higher rather than lower doses of methadone, and longer rather than shorter periods of treatment. It is less clear on the role of ancillary services. It would appear, on the available evidence, that highly intensive services are *not* warranted as a part of routine methadone maintenance treatment. Drug counselling and primary health care services nonetheless improve effectiveness.

Methadone is generally safe when used as a long-term maintenance medication. However, there are risks associated with the first two weeks of treatment and with diverted methadone in terms of an increased risk of death due to methadone overdose. These risks are small compared with the benefits that accrue from making the treatment available, and can be minimized by the proper training of medical practitioners and by restricting take-home methadone to those patients who are managing their medication responsibly. Education of patients and illicit drug users about the safe use of methadone would also help with both these problems. In conclusion, the accumulated results of nearly four decades of research suggests that methadone maintenance treatment is an effective treatment for opioid dependence, and that its widespread application throughout the world is a good example of an evidence-based intervention for the treatment of drug dependence.

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