# Methadone: where are we now?

*John A Henry*

***Methadone is now widely used as opioid replacement therapy because it reduces crime and prevents spread of disease by the intravenous route. However, it is potentially toxic, especially to drug naive patients, and requires careful prescribing.***

The mention of methadone generates a wide range of reactions and opinions, many of them poorly informed. Methadone, the most widely studied treatment for heroin addiction, currently has a favoured place in the management of opioid dependence. However, despite its popularity, it has serious disadvantages. With so many patients under treatment, every doctor needs to know about methadone.

## HISTORY

Methadone, a moderately potent synthetic opioid drug patented in Germany in 1941, was introduced as an analgesic in the UK in 1947. Although included in the British National Formulary (BNF) (British Medical Association and the Royal Pharmaceutical Society of Great Britain, 1998) as an analgesic for severe pain and as a cough suppressant in terminal disease, its best known use lies in the management of opioid addiction.

This history goes back to 1963, when methadone was proposed by Nyswander and Dole in the USA as a maintenance treatment for the management of heroin addiction. They mistakenly thought that it reversed a metabolic dysfunction caused by drug addiction and considered large doses of methadone (80–150 mg daily) to be necessary, believing that if addicts (on the programme) tried heroin again they would not achieve euphoria and so would have no incentive to leave the programme (Liappas et al, 1988).

However, reports worldwide confirmed that methadone maintenance treatment was highly effective in the management of heroin-dependent patients. A Hong Kong study compared patients kept on methadone with those in which methadone was gradually replaced by placebo under double-blind conditions. By the end of 3 years the placebo group were 63 times more likely to have been discharged from treatment because they had returned to heroin use (Newman and Whitehill, 1979). A Swedish report showed that addicts given methadone for 2 years were 38 times more likely to have stopped regular illicit drug use than those given no treatment (Gunne and Gronbladh, 1981). In the 1970s, UK clinics began to use oral methadone instead of injected heroin in their drug-withdrawal programmes.

With the steep increase in heroin addiction during the 1980s and 1990s, and the rise in human immunodeficiency virus (HIV) infection as a result of intravenous drug use, methadone was increasingly seen as the best way of controlling the problem. The idea is to replace the user's requirement for the abused drug, usually heroin, with methadone, taking advantage of many properties of methadone which support its use as replacement therapy. The use of methadone as the major drug for opioid replacement therapy is now widespread, with 250 000 patients under treatment on the drug in Europe alone.

## PHARMACOLOGICAL PROFILE

Most of the reasons behind the use of methadone as maintenance treatment for heroin addicts lie in its pharmacological profile, which gives it advantages but also disadvantages. The most immediate advantage is its long elimination half-life (in the region of 12–48 hours), so that its opioid agonist effect persists for over 24 hours. This means that the drug needs to be administered only once a day to prevent opioid withdrawal symptoms. This contrasts with the 1–2-hour half-life of diamorphine which makes

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several injections each day a major requirement of the addict's lifestyle. However, the disadvantage of this is that symptoms following withdrawal of methadone are more prolonged and are also said to be more severe than heroin withdrawal symptoms (Gossop and Strang, 1991), in keeping with the longer persistence of methadone in the body.

Another major advantage is that methadone can be (and is in practice most commonly) prescribed orally as a non-injectable syrup. While most non-injectable or 'non-abusable' formulations of other drugs have not lived up to their promise, it appears that methadone's liquid formulation successfully defies amateur attempts to render it injectable, although this does not apply to the tablet formulation. However, for those who consider that their patients who are established intravenous drug users need to inject methadone, an intravenous formulation is available.

Methadone taken orally does not produce a subjective 'high' or any clinically apparent behavioural impairment, although many addicts complain that their level of wellbeing is lower when on the drug. Once established on methadone, toxic effects are extremely rare unless the patient indulges in abuse of other substances, which is a common problem.

## PERSONAL AND SOCIAL ADVANTAGES

The main advantage to the user is that the use of illicit heroin is reduced or discontinued; risks associated with intravenous drug use are diminished, general health improves and the patient is given the opportunity to develop a more stable and positive lifestyle. Patients within a treatment programme are also less likely to die of opioid-related problems. One study reported that the mortality rate among addicts in a methadone programme was 1.4%/year (all causes) compared with 4.8% in addicts on the waiting list (heroin overdose deaths only) (Gunne and Gronbladh, 1981).

The most important advantage to society of the use of methadone is that once users are put on replacement therapy, the crime rate goes down (Bell et al, 1992). A further advantage of methadone is that all supplies produced come through licit manufacture, so that manufacture and prescribing can be closely controlled, thus side-stepping many of the arguments levelled against illicit drug production.

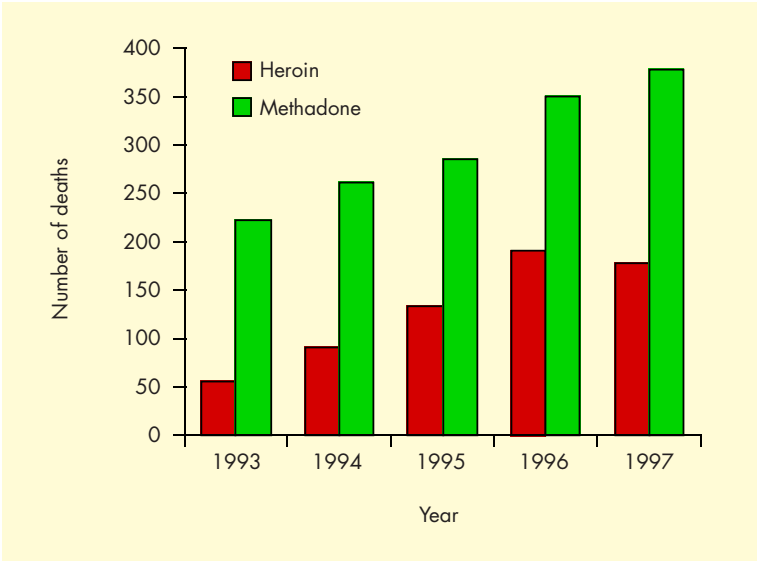


*Figure 1. Deaths involving heroin and methadone. From Office of National Statistics England and Wales 1993–97.*

## TOXICITY: A MAJOR DRAWBACK

While heroin is a toxic drug which can and does cause death from overdose, methadone is also toxic, and a number of reports have drawn attention to rising numbers of deaths from methadone (Marks, 1994; Clark et al, 1995; Cairns et al, 1996; Williamson et al, 1997). British figures show that while the number of deaths attributed to heroin rose from 55 to 169 between 1993 and 1997, those for methadone rose from 220 to 368 (*Figure 1*). However, it should be noted that these figures do not include deaths registered as being due to morphine which are also very likely to be due to heroin.

It is clear that measures need to be implemented to prevent these deaths, each of which has originated as a result of methadone prescribing by medical practitioners in Britain. The number of deaths which occur from overdose in intolerant compared with tolerant users is not known, although it seems very likely that deaths are rare in people who have been taking the drug regularly for a few weeks. Many deaths arise from diversion of supplies (the illicit sale of prescribed medication to another for gain).

In Australia, half of those who died were not prescribed the drug (Williamson et al, 1997). A system of enquiring into each death and providing feedback for the doctors who had attended to the patient in the 2 weeks before death was recently set up in Glasgow. This led to a large reduction in methadone-related deaths (RTA Scott, personal communication, 1998). It is clear that closer monitoring of prescribing practice is needed, and supervised administration of the drug should be more widely implemented.

A major problem with methadone is the narrow difference between a dose and an overdose.

This is especially true for the non-tolerant user. For example, a single oral dose of 60 mg of methadone may well kill a non-tolerant individual, while the same dose is a typical replacement dose for many tolerant users. The lethal dose is even lower if methadone is taken with alcohol or benzodiazepines.

## USE IN HOSPITAL MEDICINE

In the section on opioid dependence, the BNF (British Medical Association and the Royal Pharmaceutical Society of Great Britain, 1998) warns that methadone should only be prescribed for those who are physically dependent on opioids, and recommends an initial dose of 10–20 mg daily (10–20 ml syrup), increased by 10–20 ml daily until there are no signs of withdrawal or intoxication; the dose reached is the maintenance dose.

Hospital doctors other than those working in drug dependence clinics are not usually faced with this scenario. They will meet a patient who claims he/she is on methadone and needs a dose urgently — should they prescribe it on the word of the patient? The answer is no — not without checking with the patient's clinic or GP. These cases rarely occur in the cold light of day; the clinic or GP will be uncontactable at 2 am. Again, methadone should not be prescribed — its long half-life allows for a considerable period of time (usually 48 hours or more) before any signs of withdrawal become apparent. Even if the patient is showing signs of withdrawal it is still safer to give a holding dose of dihydrocodeine (60 mg) until the history and regular methadone dosage can be checked.

In the general practice and drug dependency unit settings, the main constraint is to know whether the patient is dependent on heroin or not. If the patient is dependent, treatment is commenced and the patient is stabilized on methadone. A new set of guidelines on the management of drug misusers soon to be released by the Department of Health should be of help to all doctors involved with patients receiving or requiring methadone.

## OVERDOSE

Three categories of individuals are at particular risk of methadone overdose. Methadone, even in low doses, is a special hazard for children who may ingest drugs left carelessly in the home or which may be maliciously administered, and close observation and appropriate treatment are urgently needed to prevent a fatal outcome. Non-tolerant adults are at risk — whether taking it for abuse or whether they have falsely claimed they are dependent. Tolerant adults are at risk if they overdose or suffer an interaction by also taking alcohol, benzodiazepines or heroin.

The first step in management of overdose is to ensure that the airway is open and that respiration is adequate — the degree of toxicity is apparent from the degree of respiratory slowing. Ventilatory support is urgently needed if respiration is very slow or has arrested; full cardiopulmonary resuscitation will be required for cardiac arrest. Once ventilation has been assessed, naloxone may be given intravenously or intramuscularly depending on the degree of urgency. The question arises as to how long the patient should be observed because of the long half-life of methadone. If respiration as measured by respiratory rate is adequate 4 hours after the last dose of naloxone, the patient can be considered suitable for discharge from the medical point of view.

## ALTERNATIVE MEDICAL TREATMENTS

Although a number of alternatives to methadone have been proposed, none has yet been conclusively shown to be better than methadone. For example L-alpha-acetylmethadol (LAAM) may be effective in certain situations. However, in a direct comparison, methadone-treated subjects were more likely than LAAM-treated subjects to remain in the treatment programme and less likely to discontinue because of side-effects (Glanz et al, 1997).

Dihydrocodeine appears to be an effective and safe drug of replacement (Robertson, 1996). Buprenorphine is used by some workers, but may not be more effective than methadone (Ling et al, 1996), although it may be better than methadone for controlling cocaine abuse in individuals dependent on opioids (Foltin and Fischman, 1996). Clonidine and lofexidine act centrally to minimize opioid withdrawal symptoms. Lofexidine has less of a hypotensive effect and is an effective way of achieving withdrawal (Bearn et al, 1996).

## CONCLUSION: WHERE WE ARE NOW

Some see methadone replacement therapy as the answer to heroin abuse. Crime is reduced, use of other illicit drugs diminishes (but does not necessarily disappear), and many patients return to gainful employment. But in many cases the benefits only last as long as the maintenance treatment continues, and methadone should not be seen as a pharmacological alternative to rehabilitation of the drug user, which

should be a prime objective. The most stark drawback is the fatal toxicity of methadone, which currently kills as many or more people than heroin. This needs to be reduced; close adherence to prescribing guidelines and supervised administration appear to be the most immediate answers.

Methadone is not a panacea. Many of the advantages of replacement therapy are not necessarily specific to methadone, and could possibly also be claimed for other methods or drugs. At present, many of the advantages of opioid replacement therapy have only been clearly demonstrated with methadone. The ideal drug for managing opioid dependence should be safer for administration to tolerant individuals and following overdose. Perhaps the greatest difficulty does not lie with the drugs: effective rehabilitation is labour-intensive and costly. HM

### KEY POINTS

- Methadone replacement therapy is the most widely used treatment for managing opioid dependence.
- Methadone should only be used for opioid-dependent patients and has no place in managing the chaotic drug user.
- Its use reduces spread of infections from intravenous injection and brings down the crime rate.
- When a patient on treatment comes under hospital care, methadone should only be given after confirming the dose with the regular prescriber.
- Overdose can be fatal; the typical daily dose of 60 mg can kill a non-tolerant person. Overdose can be managed with supportive care and naloxone.


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## COMMENT

Professor Henry provides us with an authoritative and usefully balanced appraisal of the current place of methadone in the treatment of opioid dependence. There are two comments which I would like to make by way of footnote.

First, I would argue that within a rounded perspective and with all the provisos entered, one needs firmly to hold onto the fact that methadone is an extraordinarily valuable drug in the treatment of opioid dependence. My concern is that the data given in *Figure 1* will in some quarters be simplistically interpreted as suggesting that methadone is twice as dangerous as leaving addicts on street heroin. That would be a dangerous misreading. Methadone significantly reduces rather than increases mortality among opioid addicts as Henry himself documents.

True facts need to be highlighted, given the political attack which is sometimes today made on methadone by those who would like to go back to injectable heroin prescribing for addicts as the first-line response. And meanwhile tighter clinical policies are certainly needed so as to reduce the risk of methadone deaths, and the forthcoming Department of Health guidelines on good practice should help in this regard.

And my second point simply echoes Henry's very fair 'not a panacea' conclusion. Within the context of a positive appraisal of methadone one must caution against drug dispensing units becoming mere methadone dispensaries with concomitant alcohol and benzodiazepine misuse shrugged off, psychological treatments discounted, the social dimensions forgotten, and the plight of families not part of business. Those unhappy outcomes are side effects of methadone as a magic bullet which should be resisted. HM

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