

## REVIEW ARTICLE

# The effects of methadone and its role in fatalities

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Methadone is a synthetic opioid, used both as an analgesic in severe pain relief and now mainly in the treatment of opiate dependence. Such use of the drug has increased as its advantages have become widely recognized. There are undesirable outcomes from its greater use, including a substantial market in diverted methadone and a high number of deaths where the drug has been implicated. It is important to understand how and why methadone causes death so that such fatalities can be minimized, and to disseminate such information. This paper presents an overview of the chief effects of methadone on the human body, considering its metabolism, drug interactions and tolerance. The principal mechanisms by which methadone causes death are discussed: respiratory depression, aspiration of vomit, pulmonary oedema, bronchopneumonia, cardiac problems and renal failure. Many such deaths are preventable, if drug interactions and polydrug use are avoided, its longer period of metabolism and individuals' tolerance levels are considered. It is hoped that this paper will (a) help guide health professionals in their management and treatment of patients participating in methadone treatment programmes, and (b) provide some basic information for those dealing with individuals who have consumed methadone. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — methadone; pharmacological effects; poisoning; drug-related death; drug overdose

## INTRODUCTION

Methadone is a synthetic opioid which is used both as an analgesic in severe pain relief and now mainly in the treatment of opioid dependence. It is controlled under United Nations' conventions and can only be prescribed in the UK, as in most countries, by a physician (DH, 1999; Verster and Buning, 2000; CSAT, 2004b). It is widely prescribed in oral liquid formulations and tablets. Injectable forms are also still fairly common in and almost exclusive to the UK; about 10% of all UK methadone prescriptions in 1995 (Strang and Sheridan, 2003).

## *Benefits of methadone*

Methadone is currently the preferred drug of choice for the treatment of opioid dependence in many countries, including the UK (Verster and Buning, 2000). Methadone dominates the substitute opiate-prescribing market in the UK, accounting for perhaps 90% of it (Strang and Tober, 2003). Within the EU the number of addicts being treated with methadone increased seven-fold between 1993 and 2000 (EMCDDA, 2000). Such use of the drug has increased as its advantages have become widely recognized: reducing criminal activity (Gossop *et al.*, 2001) and the costs of crime (Godfrey *et al.*, 2004) and illicit drug use by opiate addicts (Marsch, 1998); improving social integration (Metrebian *et al.*, 1998) and employment prospects (Coid *et al.*, 2000); and reducing the morbidity (Ball *et al.*, 1988; Ward *et al.*, 1992; Coplehorn *et al.*, 1993; Wilson *et al.*, 1994; Ward *et al.*, 1999) and mortality of opiate users (Coplehorn *et al.*, 1996; Risser *et al.*, 2001).

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*Deaths involving methadone*

Deaths from methadone have been reported over the past 30 years or more from a range of countries where methadone is prescribed: Australia, Germany, Sweden, Switzerland, the Netherlands, the UK and the USA (Baden, 1970; Gardner, 1970; Fugelstad *et al.*, 1995; La Harpe and Fryc, 1995; Williamson *et al.*, 1997; Heinemann *et al.*, 2000; Karch and Stephens, 2000; Perret *et al.*, 2000; Valmana *et al.*, 2000; Zador and Sunjic, 2000; Squires *et al.*, 2001; Buster *et al.*, 2002; Oliver *et al.*, 2002; Bryant *et al.*, 2004; CSAT, 2004b).

There are two main types of source in the UK for regular information on 'acute' drug-related deaths (DRDs)—three General Mortality Registers (GMRs) and one Special Mortality Register (SMR). The GMRs are the General Register Offices for England & Wales, Scotland, and Northern Ireland. The essential mortality data recorded by these Offices are derived from medical death certificates. In England & Wales and Scotland some supplementary information is provided. The details of substances recorded by the GMRs are those recorded on the death certificate. No detailed information is passed to them on toxicology, e.g. levels of drugs and/or alcohol found in body tissues, blood or urine. Post-mortem reports are not provided to the GMRs. Special drug poisoning databases have been established by the GMR for England & Wales (Christophersen *et al.*, 1998) and the GMR for Scotland (Jackson and Cole, 2000). These government agencies publish annual statistics on DRDs. The GMR in Northern Ireland does not currently publish information on such cases. However, data are collated at a UK-level on DRDs by the lead author on behalf of the Department of Health in its role as the UK focal point for the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).

At present, there is only one SMR in the UK that publishes information on DRDs—the National Programme on Substance Abuse Deaths (np-SAD) at St George's Hospital Medical School (Ghodse *et al.*, 2003). Their coroners' database was started in July 1997, and now contains records on more than 8000 cases. Information from this database is published in both 6-monthly and annual reports on cases notified voluntarily by coroners in England and Wales. Coverage now extends to about 95% of all jurisdictions. Some coroners in Northern Ireland, the Isle of Man and the Channel Islands, as well as some Procurators Fiscal in Scotland, have started to submit information to the Programme. In addition to the information contained on death certificates, the database receives

further demographics, medical history and other details of the deceased and the circumstances of their death. In recent months, some coroners have started to include information on toxicology on their returns.

Information from the Programme is also submitted to the EMCDDA. Information from both the GMRs and the SMR are subsequently published so as to inform medical professionals, policy-makers, service providers, epidemiologists and others concerned with the prevention and reduction of DRDs (Bellis *et al.*, 2004; EMCDDA, 2003).

The mortality statistics quoted below are derived from published sources and from supplementary unpublished data provided specifically for this project from the three GMRs above. Deaths where methadone was mentioned on the death certificate in the UK rose from 255 in 1993 to peak at 499 in 1997. They fell back to 279 in 2001 but then rose again to 316 in 2002 (Griffiths *et al.*, 2002; Griffiths, 2003 and 2004; Jackson, 2002 and 2003; personal communication, Fegan G, Department of Finance & Personnel, Northern Ireland, 14 January 2003 and 2 February 2004). Most of these were in England and Wales where the total rose from 232 in 1993 to 421 in 1997, fell to 207 in 2001 before rising to 216 in 2002. This demonstrates that there is no guarantee that trends in methadone-related deaths will necessarily continue in a predictable way.

Between 1993 and 2002 there were 3604 deaths in the UK where methadone was mentioned on the death certificate out of a total of 32276 notified to the General Register Offices during this period, using a broad definition including such substances as paracetamol, antidepressants, etc. This represents 11.2% of all such deaths, and is consistent with the patterns found in data from the np-SAD. Published figures from this Programme show that, for example between 1999 and 2002, the overall proportion of cases where methadone was found at post-mortem was similar to that reported by the General Register Offices (Ghodse *et al.*, 2000, 2001, 2002, 2003). The specific percentages are: 1999—11.0% (147/1340); 2000—6.6% (85/1284); 2001—10.8% (94/872); and 2002—11.5% (98/853). In such a context it is important to know more about the nature of how these deaths are occurring.

The fact that methadone was mentioned on the death certificate does not imply it was necessarily implicated as the cause of death. For example, a recent study of 352 sudden unexplained deaths in the west of Scotland between 1991 and 2001, in which methadone was detected at post-mortem, concluded that 23% of these cases were not associated directly with

the toxic effects of methadone whether alone or in combination with other drugs and/or alcohol (Seymour *et al.*, 2003).

#### *Methadone prescribing and diversion*

Over the past decade the number of methadone prescriptions dispensed in Scotland increased 11-fold (Seymour *et al.*, 2003); in England the number of times methadone mixture was prescribed rose 65-fold between 1980 and 2000 (personal communication, Department of Health, Statistics Division 1E, Prescription Cost Analysis system). Seymour *et al.* (2003) have attributed the rise in methadone-related deaths during the 1990s to the increased prescribing of the drug for the treatment of opioid dependence. However, the introduction of supervised consumption appears to have helped to reduce the number of fatalities. Despite this, there is still a significant number of deaths to which methadone may have contributed.

There is a substantial 'grey'/black market in all forms of diverted methadone. The problem of diversion is not restricted to the UK (Fountain *et al.*, 2000; Corkery, 2002; Corkery and Airs, 2003); similar issues exist, for example, in Australia and the USA (Caplehorn and Drummer, 1999; Karch and Stephens, 2000). The type of formulation being diverted varies from country to country. For example, in the UK it is principally liquid methadone that is seized by the police (Cairns *et al.*, 1996). In recent years it is methadone tablets for pain management dispensed by pharmacists that US police have increasingly seized. This increase is also associated with increased prescribing of oral methadone for the outpatient management of chronic pain rather than take-home supplies of methadone dispensed to patients in methadone maintenance treatment (MMT) (CSAT, 2004b). This issue is also a concern in Australia (Williamson *et al.*, 1997). The role of methadone tablets (which are not prescribed for opioid dependence) in UK methadone fatalities is not known. The proportion of methadone seizures made by UK police accounted for by them fell from 22% in 1997 to 12% in 2000; the proportion accounted for by liquid methadone rose from 63% to 73% over the same period (personal communication, Home Office Research Development and Statistics Directorate, 1 June 2003).

Diversion may be a factor in many methadone-related fatalities (Cairns *et al.*, 1996; Zador and Sunjic, 2000; Gagajewski and Apple, 2003). At least three-fifths of deaths associated with methadone in England and Wales are accounted for by the use of methadone which may have been illicitly obtained

(Ghodse *et al.*, 2003). Rates as high as 75% have been reported in Scotland (Fiddler *et al.*, 2001).

Given the background outlined above it is important to understand how and why methadone causes death so that the frequency of such fatalities can be minimized. This overview aims to present the chief effects of methadone on the body, consider its metabolism, drug interactions, tolerance and how it causes death. This overview is to help guide health professionals in their management and treatment of patients participating in methadone treatment programmes, or where methadone is administered for pain relief.

The literature reviewed here was identified from internet searches, including Medline, conducted using English (and some French) language keywords. The search terms used, either alone or in combination, included the following or their French equivalent: methadone; pharmacology; poisoning; overdose; fatality; lethality; drug-related death; metabolism; drug tolerance; drug interactions; mechanisms of death.

## METABOLISM OF METHADONE

### *Pharmacokinetics*

Methadone appears in the blood stream within 30 min of being taken orally and has a bioavailability of between 70% and about 90%. It takes 2 to 4 h for it to reach peak plasma concentrations (Eap *et al.*, 2002). The analgesic effect of methadone sets in about 15 min after subcutaneous injection. Methadone has a long but variable plasma half-life. Mean estimates of this have varied from 15 to 55 h (Wolff *et al.*, 1997) but it is usually assumed to be 24 h. In some drug-naïve persons, a single dose can have clinical effects up to 72 h in duration (Olsen *et al.*, 1997). When methadone is the principal source of death it is likely that death will occur a few hours following its consumption.

### *Metabolism*

Methadone is widely distributed amongst tissues. It is highly bound to tissue proteins, perhaps in the range 60%–90%; this may help to explain its cumulative effect and slow elimination (Biodone, 1999). The main binding protein in plasma is  $\alpha$ 1-acid glycoprotein. Methadone is chiefly metabolized in the liver, where it undergoes N-demethylation and cyclization, and appears to be eliminated unconjugated. The major metabolites of methadone (EDDP and EMDP) are widely considered to be pharmacologically inactive;

the free (unbound) pharmacologically active fraction of the total drug in plasma is very small, ranging from 6% to 14% (Wolff, 2003). These metabolites are excreted in the faeces (via bile) and urine together with any unchanged methadone. Excretion is by glomerular filtration and renal reabsorption also occurs. Unchanged methadone may also be stored in the liver, where it is bound non-specifically and released again chiefly unaltered (Methadone syrup, 1999).

#### *Factors affecting methadone metabolism*

Drug users with severe liver damage may have decreased ability to metabolize opioids. For example, one study found the period of terminal half-life to be 18.8 h in those with healthy livers and 35.5 h for those with chronic liver disease (Novick *et al.*, 1981). Care should therefore be taken when administering methadone to patients with hepatic impairment, since methadone plasma levels will be elevated and pose an overdose risk.

Methadone takes 2 to 3 weeks to induce itself (Rostami-Hodjegan *et al.*, 1999), and thus the hepatic enzyme systems (which convert methadone to its metabolites) of new methadone users will therefore take longer to clear methadone from their bodies (Karch and Stephens, 2000). It has been shown that the metabolism of methadone is very slow in individuals who have just started titration with the drug and/or are methadone-naïve. For example, Wolff *et al.* (2000) found that clearance of methadone was significantly lower in opiate addicts at the start of treatment (median elimination half-life 128 h) than in those who had reached the steady-state level (median elimination half-life 48 h). Methadone thus stays in the blood much longer than anticipated. The drug accumulates from one dose to the next. This, clearly, poses a risk of overdose especially during the initial phase of MMT (Drummer *et al.*, 1992; Caplehorn, 1998; Sunjic *et al.*, 1998; Caplehorn and Drummer, 1999; Milroy and Forrest, 2000; Wolff *et al.*, 2000).

#### *Genetic variability*

There may be genetic variability in the response of a sub-group of individuals to the drug and their metabolism of it, making them more susceptible to overdose (Robinson and Williams, 1971; Nakamura *et al.*, 1982; Eap *et al.*, 1999). There can be great variation between individuals in the accumulation and clearance of methadone from their bodies. Bioavailability has been reported to vary between 41%

and 99%, its half-life to vary between 4 and 91 h, and its rate of clearance from the body has been reported to vary by a factor of almost 100 (Hall *et al.*, 1999).

Eap *et al.* (2001, 2002) have distinguished three types of metabolizers in respect of a genetic polymorphism of cytochrome P450 2D6 which assists in the processing of methadone—poor (zero functional gene), extensive (one or two functional genes) and ultra rapid (three or more functional genes). Further variation is evident amongst those in MMT; the genotype of some clients may exhibit a different pattern of CYP2D6 activity when methadone is present (Shiran *et al.*, 2003).

The cytochrome P450 3A4 enzyme system (CYP3A4) is the principal agent responsible for metabolizing methadone (Iribarne *et al.*, 1996). The other main enzymes responsible are CYP 2D6 and CYP 1A2. Other enzyme families such as CYP 2B6, CYP 2C19 and CYP 2C9 appear to be less important although their exact role and that of variability between individuals are both under investigation (Foster *et al.*, 1999; Eap *et al.*, 2001; Moolchan *et al.*, 2001; Borg and Kreek, 2003; DeMaria, 2003; Wang and De Vane, 2003; Gerber *et al.*, 2004). Strong evidence suggests that any substance that interacts with the CYP3A4 enzyme could precipitate an interaction with methadone (see below) including other metabolic proteins (Dresser *et al.*, 2000; Eap *et al.*, 2002).

#### *Precautionary measures for administering methadone*

Methadone should only be administered following a thorough clinical assessment of opioid dependence and the current level of drug consumption. There is now widespread agreement that for outpatient stabilization the initial dose of methadone will be less than 30 mg (DH, 1999; Verster and Buning, 2000; CPO, 2001). The Department of Health *Orange Guidelines* (DH, 1999) and the *European Methadone Guidelines* (Verster and Buning, 2000) recommend that where tolerance to opioids is high the normal dose will be between 25–40 mg and that where tolerance is low or uncertain an appropriate dose would be between 10–20 mg. Ghodse (2000) also supports the latter approach in case the severity of dependence has been exaggerated and the patient cannot, in reality, tolerate a high dose. Titration of methadone doses is of paramount importance in avoiding the risk of overdose (DH, 1999). The *Orange Guidelines* suggest small increases in dosage of 5 to 10 mg/day when patients are commencing a course of MMT.

It is also important to remember the potential effects on methadone metabolism when discontinuing medications. For example, methadone serum levels may decrease in the days following the stoppage of drugs that inhibit CYP enzymes, causing withdrawal that needs increased methadone. If a CYP inducing medication is stopped, methadone serum levels may rise to toxic levels unless careful methadone dose reductions are implemented (Leavitt, 2004).

## DRUG INTERACTIONS

Overdose deaths solely due to methadone are still relatively rare events (Schwartz *et al.*, 1999; Ghodse *et al.*, 2003; Seymour *et al.*, 2003; Griffiths, 2004). It is therefore important to consider the effects of other substances taken concurrently.

### *Methadone inducers*

The metabolism of methadone can be affected by interactions with other medications such as phenytoin, carbamazepine, rifampicin, fluconazole and some protease inhibitors. These types of drugs cause induction of the CYP3A4 enzyme (whereas drugs such as paroxetine induce the CYP 2D6 enzyme) and an increase in the metabolism of methadone and thus a decrease in its concentration. This lessens the risk of methadone-induced overdose but causes other clinical problems, mainly the onset of withdrawal symptoms (Finelli, 1976; Kreek *et al.*, 1976; Bending and Skacel, 1977; Tong *et al.*, 1981; Liu and Wang, 1984; Raistrick *et al.*, 1996; Eap *et al.*, 2002).

The concurrent administration of drug inducers such as benzodiazepines, barbiturates and opiates with methadone may result in significantly lower plasma levels of the drug (Schall *et al.*, 1996). This in turn may trigger withdrawal symptoms and lead to individuals in MMT seeking (extra) illicit drugs or prescription drugs especially benzodiazepines to alleviate their symptoms, i.e. increased 'instrumental drug utilization' (Best and Ridge, 2003). In this way although the risk of overdose from methadone may be reduced, the risk of overdose *per se* is not diminished. This risk is further compounded by the fact that the effects of inhibitors are transient, and thus plasma levels of methadone will increase again.

### *Methadone inhibitors*

Ketoconazole and erythromycin may (because they inhibit the metabolism of methadone) enhance the risk of overdose in susceptible people if taken concurrently.

Fluoxetine can increase the plasma concentration of methadone (Furet *et al.*, 1999), as can other selective serotonin reuptake inhibitors such as fluvoxamine (Bertschy *et al.*, 1994; Eap *et al.*, 1997; Cobb *et al.*, 1998). These act as substrates or inhibitors of the CYP3A4 enzyme. The effects of inhibitors are transient, lasting a few days compared with the length of time that induction (2 or 3 weeks) can take (Wolff *et al.*, 2000).

### *Other interactions*

Other interactions have been reported. Of particular importance are monoamine oxidase inhibitors (MAOIs). These can prolong and potentiate methadone's respiratory depressant effects. Used with opioids including methadone, MAOIs may cause fatal hypotension and coma (Methadone syrup, 1999). Other centrally acting agents enhance the general depressant effects of methadone through synergism; these include alcohol, barbiturates, phenothiazines and tranquillizers (Kreek, 1986; Nestler, 1996; Quinn *et al.*, 1997; Payte and Zweben, 1998; Gourevitch, 2001; Kramer, 2003). Furthermore, some psychotropic drugs may increase methadone's analgesic effects.

### *Physical and chemical incompatibilities*

Injectable preparations of methadone are regarded as physically and chemically incompatible with a number of solutions, including preparations of drugs such as aminophylline, ammonium chloride, amobarbital, chlorothiazode sodium, phenytoin sodium, heparin sodium, methicillin sodium, pentobarbital sodium, phenobarbital sodium and thiopental sodium (Patel and Phillips, 1966), as well as everyday substances such as sodium bicarbonate (Methadone injection, 1999). Pharmaceutical/chemical reactions occur between these substances and methadone hydrochloride and lead to a number of consequences: (a) the mixture of solutions with different pH values; (b) new substances are formed, and these may have undesirable or unwanted reactions; (c) these substances may precipitate out in the syringe and pose a risk of blocking veins on injection.

Doses of methadone therefore need to be adjusted to take account of such influences, and also of the impact of methadone on other drugs. For more comprehensive reviews of drug interactions with methadone see DeMaria (2003) and Leavitt (2004).

## TOLERANCE

Tolerance, or rather the lack of tolerance, is a key factor in methadone-related overdose. This section

considers aspects of tolerance and its role in fatalities, and what constitutes a fatal level of methadone.

Amongst the more common adverse effects of methadone are lightheadedness, dizziness, anorexia, nausea and vomiting, dry mouth and sweating (Wolff, 2002). Similar to other opioids, methadone toxicity can cause drowsiness and hypotension. True intolerance to methadone is considered to be most unusual: if, very rarely, an allergic reaction occurs alternative drugs can be used in treatment of dependence (Uehlinger and Hauser, 1999).

The largest proportion of deaths associated with methadone amongst patients undergoing treatment for drug dependence has occurred during the period of the induction of the drug. This usually happens when either the patient's tolerance to opioids is over-estimated or the patient is also consuming other opioids or CNS depressant drugs (Harding-Pink, 1993; Davoli *et al.*, 1993; Caplehorn, 1998; Karch and Stephens, 2000). Other drugs are usually detected at post-mortem when deaths occur at the later stages of treatment for dependence (Appel *et al.*, 2000).

The ability of individuals to tolerate different quantities of methadone depends, in part, on their degree of previous exposure to opioids. Whilst there is usually cross-tolerance between opioids, it can be incomplete. For example, asymmetries in cross-tolerance between methadone and other  $\mu$  opioid receptor agonist analgesics such as morphine, codeine and dextropropoxyphene have been reported and explained in terms of heterogeneity in opioid receptor mechanisms (Neil, 1982; Ivarsson and Neil, 1989; Crews *et al.*, 1993).

#### *What is a fatal level of methadone?*

A number of studies have found fatal post-mortem (blood) concentrations in the range 0.2 mg/l–4.5 mg/l, with the mean ranging from 0.772 mg/l to 1.371 mg/l (Milroy and Forrest, 2000). In a comparison of intravenous and oral administration, the ranges of concentrations were similar. However, the means were significantly different: that for intravenous cases was 1.1 mg/l compared with 0.393 mg/l for oral cases (Segal and Catherman, 1974).

A fatal dose for a novice/naïve or non-tolerant person may be the same or lower than an individual undergoing MMT. Worm *et al.* (1993) found that the blood methadone level for fatalities who were not in a maintenance programme was almost half that of those in treatment (median 0.22 mg/l vs 0.43 mg/l; mean 0.27 mg/l vs 0.47 mg/l). They also found that when alcohol was present (blood alcohol levels above 50 mg/100 ml), the level of methadone needed to

cause death was significantly lower than when only methadone was present post-mortem (median 0.15 mg/l vs 0.28 mg/l; mean 0.25 mg/l vs 0.43 mg/l).

However, it has to be borne in mind that methadone quickly disperses into tissues after ingestion as it is highly lipophilic and gives rise to typically low plasma concentrations (Dole and Kreek, 1973). As a result, the blood levels of methadone found at post-mortem for deceased who were in MMT programmes are unlikely to be high. A strong correlation ( $r=0.82$ ,  $p<0.001$ ) between methadone dose and trough plasma concentration has been reported (Wolff *et al.*, 1991). However, this correlation is dependent on good compliance with the MMT programme for those patients who have not attained a steady-state condition. Furthermore, only about 80% of the observed variability in methadone plasma concentration can be explained by the dose consumed (Wolff *et al.*, 1991). It has been argued that this relationship may not be linear (Dorsey, 2003; CSAT, 2004a). Therefore the plasma concentration of methadone for MMT patients may not be directly related to their prescription dosage. On occasion, observed levels for those in such programmes have been found to be below the toxic level for opioid-naïve individuals (Robinson and Williams, 1971).

Some writers have suggested that a lethal dose of methadone amongst non-dependent subjects is between 0.8 and 1.5 mg/kg of body mass, 50 mg for adults on average and 10 mg for children (Moffat *et al.*, 1986; Eliez, 1997). However, other researchers consider these doses to be too high (Wolff, 2002). The dose that will probably cause death in a naïve adult is at the bottom end of the range for a single day's maintenance dose for a tolerant addict (Harding-Pink, 1993). This is underlined by the fact that it is generally accepted within forensic circles that a serum methadone concentration of over 0.4 mg/l is enough to cause death from respiratory depression, yet levels of up to 1 mg/l have been found in living patients receiving treatment (Loimer and Schmid, 1992; Merrill *et al.*, 1996; Hendra *et al.*, 1996). Some methadone fatalities have shown lower concentrations than those recorded in therapeutic treatment.

Heinemann *et al.* (2000) found that those with a history of treatment had higher blood methadone levels than those outside treatment: treatment mean 0.62  $\mu$ g/ml (median 0.45, SD 0.5, range 0.09–2.0); outside treatment mean 0.43  $\mu$ g/ml, (median 0.26, SD 0.61, range 0.5–3.5). Blood levels below 0.4  $\mu$ g/ml were found in 48% of all poisonings amongst the treatment group, compared with 68% in the non-treatment group. Where methadone was the sole substance detected,

blood levels were in the range 0.25–1.38 µg/ml for those with a treatment history and 0.26–0.55 µg/ml amongst those with no history of treatment. These results confirm the greater susceptibility of those not in treatment to methadone overdose, but also show the high variability of inter-individual tolerance levels.

#### MECHANISMS OF DEATH IN METHADONE-RELATED FATALITIES

As a synthetic opioid, methadone causes death in a similar way to heroin (White and Irvine, 1999). However, Wolff (2002) makes the point that what sets methadone apart from other opioids is its potential for delayed toxicity. The signs of overdose associated with methadone include deep respiratory depression, unusually loud snoring, pin-point pupils, hypotension, circulatory failure, pulmonary oedema and coma. The following symptoms have been observed in children: drowsiness, limpness, pin-point pupils and apnoea. The principal mechanisms for methadone-related deaths are discussed below.

##### *Respiratory depression, airway obstruction, pulmonary oedema and bronchopneumonia*

Respiratory depression is the probable mode of death when a user is found with evidence of a recent injection. The drug depresses the brain stem's respiration control centre, reducing its sensitivity to carbon dioxide (CO<sub>2</sub>). If a user does not inhale sufficient oxygen, cardiac arrest and low-oxygen brain damage (hypoxia) can result. Respiratory depression develops 12–14 h after ingestion of methadone, particularly in those who have had or have only a weak tolerance to the drug (Kreek, 1978; Drummer *et al.*, 1992). Tolerance can be lost through abstinence while imprisoned (White and Irvine, 1999; Singleton *et al.*, 2003) or by having successfully completed inpatient opiate detoxification (Strang *et al.*, 2003).

It should be noted that tolerance to an opioid's respiratory depressant effects does not necessarily develop at the same rate as tolerance to its euphoric and analgesic effects (White and Irvine, 1999). Tolerance to the respiratory depressant effects of methadone may be incomplete; thus, a sudden large and acute increase in methadone serum level can put long-term MMT patients at risk of opioid-induced respiratory depression (CSAT, 2004a).

Respiratory depression is only seen in about half of overdose cases with CNS depression (Wolff, 2002). The plasma concentration of methadone affects the

breathing pattern. Low concentration levels cause a lessening of tidal volume (i.e. the normal volume of air inhaled and exhaled) but no change in the rate of respiration. However, both tidal volume and respiratory rate are reduced at higher plasma concentrations (Santiago and Edelman, 1985).

Most deaths involving methadone result from respiratory depression and are more likely when the drug is used in combination with other drugs, including opiates and/or alcohol. Of particular significance in this regard are benzodiazepines which are also commonly prescribed with methadone for the treatment of drug dependence. Benzodiazepines and alcohol individually act only relatively weakly to depress the respiratory system (Skatrud *et al.*, 1988; Van de Borne *et al.*, 1997). When combined with methadone, they augment these effects of the drug (Levine *et al.*, 1995; Rogers *et al.*, 1997). Chloral hydrate and clomethiazole (formerly known as chlormethiazole in the UK), commonly used for treating insomnia and agitation especially in the elderly and gerontopsychiatric populations, also act to depress the CNS and should be avoided in combination with methadone. However, these drugs are not commonly prescribed at MMT clinics and thus are of less concern in such establishments.

There are suggestions that pulmonary dysfunction may be common amongst heroin-using populations, and hence those in methadone treatment. This factor may put such addicts at greater risk of dying because of their increased susceptibility to fatal respiratory depression. Pulmonary disease can be increased by 'chasing the dragon' (heating heroin on tin foil above a flame whilst inhaling the heroin fumes through a straw or tube as the heroin sublimates), a practice that many methadone users may have followed in their pre-treatment days. Other factors that may contribute to the likelihood of respiratory infections include poor nutrition and hygiene—often found amongst opiate users. For example, there are far higher levels of pneumonia amongst injecting drug users (Warner-Smith *et al.*, 2001) and other pathology such as asthma can also pose problems (Ghodse and Myles, 1987; Furet *et al.*, 1999).

It has also been reported that benzodiazepines may increase upper airways obstruction and thus contribute to deaths from methadone toxicity in that way (Capehorn and Drummer, 2002). Benzodiazepines act by relaxing nasal alar and pharyngeal musculature (i.e. reducing dilator tone) and depressing the cough reflex. By decreasing muscle tone in the upper airway the impact of apnoeic episodes on alveolar hypoxia, pulmonary hypertension and cardiac demand is accentuated/worsened.

Aspiration of vomit occurs due to a combination of the emetic effects of methadone and its depression of the cough reflex (the primary reason for prescribing the linctus to cancer patients). The suppression of the cough reflex can further complicate matters if users vomit, since it can lead to aspiration of stomach contents.

Pulmonary oedema is also a common cause of fatalities amongst addicts overdosing on methadone, as well as those on non-opioid drugs. It can have a relatively quick onset and thus be a major factor in death. However, it can also have a gradual onset and thus be less of a contributory factor. Therefore, it can be regarded in some cases at least as a complicating factor. Together, aspiration of vomit and pulmonary oedema may contribute to increased pulmonary morbidity and thus increased risk of possible future overdose (Warner-Smith *et al.*, 2001). Linked to pulmonary oedema is bronchopneumonia, which is commonly found in up to a half of cases (see Drummer *et al.*, 1992), but is more likely to be ascribed where only methadone is given as the cause of death (Milroy and Forrest, 2000).

#### *Cardiac problems*

Methadone can block nerve conduction through membrane stabilizing activity and this can result in complications such as cardiovascular collapse or cardiac arrhythmias (Wu and Henry, 1990). The use of one or more psychotropic drugs causing cardiac arrhythmia or cardiovascular collapse may occasionally lead to sudden death. Bradycardia and tachycardia have been reported for other opioid drugs (Ghuran *et al.*, 2001), and cardiac rhythm disorder has been associated with LAAM, a methadone analogue, in susceptible individuals (European Medicines Evaluation Agency, 2001). Under certain circumstances, methadone may have the potential to affect heart rhythm (Leavitt and Krantz, 2003).

#### *Renal failure*

Usually, opioid overdose is not considered to include acute renal failure. In most cases rhabdomyolysis and myoglobinuric acute renal failure occur secondary to previous coma or prolonged immobilization (Blain *et al.*, 1985; Weston *et al.*, 1986). However, there have been occasions when this condition has occurred as a complication of a non-traumatic rhabdomyolysis and presented in cases of methadone overdose (Nanji and Filipenko, 1983; Hojs and Sinkovic, 1992). The main point is that non-traumatic rhabdomyolysis is the

cause of renal failure in these cases, not the use of methadone.

#### CONCLUSIONS

Poisoning/toxicity or intoxication/overdose are the main mechanisms in methadone-related deaths. The risk of such deaths occurring can be increased by the presence of some pre-existing medical conditions. Methadone-related fatalities are also associated with other common mechanisms such as respiratory depression, aspiration of vomit/gastric contents, pneumonia and cardiac arrest/failure. Other mechanisms and medical conditions contribute to such deaths. Those who are in methadone treatment programmes should have their medical condition checked on a regular basis, and those with the conditions outlined above made aware of the contribution that their pre-existing conditions can make to the adverse effects of drugs, especially those that depress respiration.

Almost exclusively, deaths associated with methadone also involve a cocktail of drugs (such as alcohol, and benzodiazepines i.e. diazepam, nitrazepam, etc.) (Schwartz *et al.*, 1999; Ghodse *et al.*, 2003; Seymour *et al.*, 2003; Griffiths, 2004). They typically involve substances that enhance the respiratory depressive effects of methadone, and together form a fatal combination. It is evident that much still needs to be done in educating users of the risks associated with poly-drug use, especially of mixing opioids, alcohol, benzodiazepines and antidepressants. Some prescribed medications, such as antiepileptics, can affect methadone metabolism; both prescribers and users need to be aware of these risks.

This paper has demonstrated several distinctions between methadone naivety and opioid naivety more generally. For example, methadone's longer half-life means that it stays in the body longer than other opioids and thus plasma levels build up quicker than might be realized. The metabolism of methadone is very slow in those who have just entered MMT compared with those who have been fully induced and have attained steady-state levels. The lack of complete cross-tolerance between methadone and other opioids means that those entering MMT may have lower tolerance to methadone than they might suppose, and thus initial dosages could be too high. Such differences could help to explain some of the reasons behind methadone's fatal toxicity for naïve users or those not in MMT.

Prescribers and treatment programme managers need to be aware of and communicate to those who are opioid dependent or who are entering into MMT

the dangers of using methadone following loss of tolerance and the resumption of illicit drug use. This is particularly important to get over to those leaving prison or residential detoxification programmes. There should be regular monitoring of patients' compliance with treatment plans.

Although there are numerous deaths associated with methadone each year, many of them are preventable. Improvements in the monitoring of methadone prescribing and dispensing should help to reduce the number of deaths involving this opioid.

Finally, we feel that methadone, like any other compound, may be a toxic drug if not prescribed appropriately for individuals who are dependent. It has to be prescribed in the right amount to the right individuals and for the correct indication.

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