Problem based review: The patient taking methadone

A Arora & K Williams

Abstract

Methadone Maintenance Treatment (MMT) is an effective therapy for opioid-dependence; its use is based on a harm reduction philosophy and represents one of a range of treatment approaches for opioid-dependent individuals.

The medical literature supports MMT as a well established and cost-effective treatment for opioid-dependence that allows a return-to-normal physiological, psychological and societal functioning. The effectiveness of MMT is enhanced by psycho-social interventions such as contingency management and addressing other co-existing health and social needs. MMT saves lives and reduces violent and non-violent crime, drug use and the transmission of HIV, hepatitis C and other communicable diseases. For some people, MMT may continue for life, while others may eventually be able to discontinue and remain abstinent.

Methadone interacts with numerous drugs and prolongs the corrected QT interval (QTc) with risk of sudden cardiac death. It has a prolonged half-life and premature discharge of patients after methadone overdose may be fatal.

Each patient must be assessed, treated and monitored on an individual basis. Successful outcomes through MMT require knowledge, experience, vigilance, and diligence on the part of the physician, the patient and all of those involved in treatment.

Keywords

Methadone, Naloxone, QTc, drug interactions.

Key Points

1. Methadone has a half-life of 24-36 hours; following overdose, prolonged infusions of naloxone may be necessary and early discharge of a patient may prove fatal; mortality is reduced by observation in hospital for >24h
2. Methadone causes QTc prolongation and risk of sudden cardiac death, and interacts with a variety of other drugs.
3. If a patient is to be discharged on regular methadone this will need to be prescribed by a doctor from the local substance misuse service.
4. Failure to manage opioid withdrawal adequately may lead to behavioural disturbances, including continued illicit drug use whilst in hospital
5. Naloxone is a safe treatment for patients who are not physically dependent on opioids; for methadone- or opioid-dependent patients, sedation and intubation may be necessary to reduce the risk of naloxone-induced withdrawal.

Case Scenario

A 36 year-old intravenous drug user with no fixed abode is admitted over the weekend to an Acute Medical Unit (AMU) with symptoms of pneumonia.

He smokes heavily and admits to drinking 20-30 units of alcohol per week. There are no health records available for him as he usually resides outside the local area. He informs the acute medical team that he usually takes methadone and asks for this to be prescribed.

How should methadone be prescribed and/or initiated on the AMU?

Methadone is an oral substitute for heroin (or other morphine-like drugs) for patients who are dependent on or addicted to these drugs. Methadone is a long-acting pure μ agonist and is usually available as a 1mg/1ml solution.

The following points should be noted when prescribing methadone:

- Patients admitted who are already taking methadone should normally be continued on their usual dosage; a urine screen is helpful to confirm whether the patient is continuing to take regular opioid drugs; methadone should NOT be prescribed on refusal of a drug screen by the patient; (*see Table 1 for detection time limits).*
- To avoid Methadone Maintenance Treatment (MMT) duplication and toxicity, the hospital physician and/or hospital pharmacist should contact the patient's usual prescriber and dispenser of MMT to confirm dose and compliance, preferably prior to prescribing methadone.

Alok Arora
MRCP (UK)
Registrar in Acute Medicine
Frenchay Hospital,
Frenchay Park Road,
Bristol, United Kingdom.
BS16 1LE

Dr Karen Williams
Associate Medical Director
County-wide Specialist Substance Misuse Service (CSSMS)
2gether NHS Foundation Trust,
44 London Road,
Gloucester

Correspondence:
Alok Arora
MRCP (UK)
Registrar in Acute Medicine
Frenchay Hospital,
Frenchay Park Road,
Bristol,
United Kingdom
BS16 1LE
Email: alokjarora@hotmail.com

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Table 1. Time Limits for detection of various drugs in the urine.

Drug	Days since last consumption
Heroin, morphine & other opiates (buprenorphine not routinely detected)	2-4 days
Cocaine	2-3 days
Amphetamines	2-4 days
Cannabis	Up to 1 month
Benzodiazapines	Up to 2 weeks
Methadone	5-7 days

- If a patient is methadone-naïve, or the current prescribed dose is unknown, a starting dose of 30ml (30mg) once daily is a low safe dosage which can be titrated if required.[5] This dose can also be used in a critical care setting whilst weaning patients off morphine infusions to avoid withdrawal.
- The patient should be assessed for the presence of withdrawal symptoms every 4h and if present, an additional 5-10ml (5-10mg) should be administered. A patient may therefore receive a maximum of 90ml (90mg) of methadone in total in the first 24 hours.
- Additional doses of methadone should be prescribed on the 'once only (STAT)' sections of the drug chart and not on the 'as required (PRN) drugs' section.
- From day 2 onwards, the total previous 24h dose can be combined into a single daily dose.
- Metabolism of methadone in patients first starting treatment may be slow initially resulting in accumulation of the drug between days 1-4. Minor adjustments to the dose may be required according to the assessment of withdrawal symptoms on subsequent days. By day 5, the patient should be established on a stable dose.

Case Scenario Continued

Despite administering 50ml of methadone, the patient appears anxious and is complaining of abdominal cramps. He is slightly tachycardic with a dry mouth and dilated pupils. He was given some codeine for back ache by the medical SHO shortly after admission.

What are the symptoms and signs of opioid withdrawal and how should pain be treated in patients taking methadone?

Opioid withdrawal symptoms generally peak at 2–3 days after the last use and usually resolve after 5-10 days although psychological symptoms of dependence can persist for weeks or months.

When a patient with opioid-dependence is admitted to hospital, it is necessary to distinguish between methadone use for maintenance of habit and methadone use for control of pain. In the acute setting, methadone should only be prescribed to prevent symptoms of opioid withdrawal and not as an analgesic. If anagesia is required for patients on methadone, weak opiates (e.g. codeine and dihydrocodeine) should be avoided, as these will compete with methadone and cause withdrawal symptoms.

Analgesia should be prescribed, using the analgesic ladder: start with paracetamol and NSAIDs and for severe pain add morphine (either IV or oral). If oramorph is used then it should be withdrawn before discharge and not dispensed as a take-out (TTO).

Symptoms and signs of opiate withdrawal are usually caused by increased release of noradrenaline, and include raised heart rate, blood pressure and respiratory rate. Flu-like 'cold turkey' symptoms including agitation/anxiety and hyperalgesia/pain sensitivity are often associated with dysphoric mood changes[5] (see Table 2)

Case Scenario continued:

The patient was given a further 30ml (30mg) of methadone over the next few hours. He was later found in bed on his back, snoring and difficult to rouse.

Table 2. Symptoms and Signs of Opioid Withdrawal.

Mild	Moderate	Severe
Runny nose	Irritability / Agitation	Severe Muscle Spasm
Nausea	Vomiting	Dehydration
Mild Anxiety	Severe Anxiety	Panic Attacks
Yawning	Hot and Cold Flushes	Severe Agitation
Loss of Appetite	Muscle Cramps	Delirium
Tremors	Tachycardia	Diarrhoea
Goose Bumps	Mild / Moderate Hypertension	Gastrointestinal spasm
Sneezing	Tachypnoea	
	Pyrexia	
	Abusive Behaviour	
	Loss of Direct Eye Contact/Dilated Pupils	

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What are the signs of methadone toxicity and which patients are at highest risk?

Definite signs of methadone toxicity may not become apparent for 5-9 hours after an overdose. MMT patients who have taken an overdose may appear relatively alert during conversation, with respiratory depression only arising during sleep.

Methadone can and does kill patients; death often occurs 5-6 hours after overdose[3] but premature discharge of patient following a methadone overdose can be lethal. Prior to death from methadone overdose, witnesses may observe euphoria, drowsiness, 'nodding-off', slurred speech, ataxia, heavy snoring and deep sleep.

Methadone has a long half life of 24-36 hours (up to 55 hours in opioid-naïve individuals), much longer than most commonly prescribed opioids. The half-life of methadone is affected by several patient factors (Table 4). Metabolism of methadone in patients new to the drug may be slow and result in accumulation; a dose that is barely adequate on day one may therefore become toxic on days 3-5.

Table 4. Patient Factors that Increase Risk of Methadone Toxicity

Recent benzodiazepine use (even therapeutic doses)
Use of other sedating drugs
Alcohol-dependent patients
Over 60 years old
Respiratory Illnesses
Taking drugs that inhibit methadone metabolism (see below)
Low opioid tolerance
Decompensated hepatic disease
Recent discharge from inpatient rehabilitation facility or prison

The period of highest risk of toxicity is during the first two weeks[5] after initiation as drug levels may increase for 5 days or more until a steady state is reached. After a period of abstinence of >3 days, a much lower dose is usually needed due to loss of habituation (Table 5).

Table 5. Initial Methadone Dosing

No risk factors and no recent abstinence from opioids: 30 mg or less
Risk factors for methadone toxicity: 20mg or less
Recent abstinence from opioids: 10mg or less

How should methadone overdose/intoxication be treated?

If there is a history of methadone overdose but the patient remains well and alert throughout their admission, they may be discharged after 12 hours of observation. If a patient is symptomatic at ANY time following methadone overdose, they must be observed for at least 24 hours from the last known ingestion.[2] Remember that patients or their friends may bring illicit drugs to hospital which, if used as an inpatient, may exacerbate methadone toxicity; communication with the patient's GP and community drug teams to discuss prescribing issues on discharge is important.

Naloxone is generally a safe treatment in patients who are not physically dependent on opioids. For methadone- or opioid-dependent patients, intubation may avoid the risks associated with sudden naloxone-induced withdrawal (see Table 6). Intubation should be considered if the respiratory rate falls below 12/minute, hypercapnic respiratory failure develops or for persistent desaturation despite supplemental oxygen, when the patient fails to respond to naloxone within 2 minutes of administration (Table 7).

Table 6. Issues with naloxone use (avoided by Intubation)

Ventricular dysrhythmias and cardiac arrest can occur with naloxone-induced withdrawal, especially if patients are withdrawing from other substances.
Patients in naloxone-induced withdrawal may become agitated and leave against medical advice
Naloxone can induce emesis.

Table 7. Naloxone dosing[1]

If the patient has severe respiratory depression, give 0.4-2.0mg of naloxone as an IV bolus.
If there is minimal respiratory depression, give in 0.1mg increments to avoid precipitating withdrawal.
If there is no response after the initial dose, give repeat IV boluses of naloxone 0.4-2.0mg every 2–3 minutes until a total of 10-20mg of naloxone has been administered
If there is no response after 10–20 mg naloxone, search for other causes of coma.
If the patient responds to naloxone, continue an IV infusion of naloxone at 2/3 of the effective bolus dose per hour.
Give a further IV bolus of 1/2 the effective dose 15–20 min after starting the IV infusion.
Titrate dose to avoid withdrawal, while maintaining adequate non-assisted respirations.

Case Scenario Continued

The patient was given amoxicillin and clarithromycin for his community-acquired pneumonia. The next day he complained of feeling dizzy and several runs of non sustained ventricular tachycardia were captured on subsequent cardiac monitoring. A resting 12-lead ECG showed an increased QTc interval of 502ms.

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Which drugs interact with methadone and what are the risks?

The following enzyme-inducing drugs may REDUCE the plasma level of methadone:

- Carbamazepine,
- Anti-retrovirals,
- Phenobarbital,
- Phenytoin,
- Rifampicin
- St Johns Wort[4]

If such drugs are introduced to a patient taking methadone, withdrawal symptoms may be precipitated and an increased dose of methadone may be required. Conversely, if any of these drugs are discontinued in a patient taking methadone, a dose reduction of methadone may be required to avoid intoxication.

The following drugs may INCREASE the plasma level of methadone:

- Fluconazole,
- SSRIs,
- Ciprofloxacin
- Macrolide antibiotics.

Prescription of these drugs in a methadone user is associated with QTc prolongation and a risk of life-threatening ventricular arrhythmias e.g. torsades de pointes. Other risk factors for QTc prolongation are summarised in Table 8. Patients should be closely monitored if the QTc interval is elevated (>440ms for men or >460 ms for women). Cardiology referral and/or methadone dose reduction should be considered when the QTc exceeds 500ms. In cases of QTc prolongation buprenorphine can be used as an alternative opioid substitute.[5] Buprenorphine is also preferred for patients at high risk for methadone toxicity as listed in Table 4.

Table 8. Risk Factors for QTc Prolongation in Patients on Methadone.[6]

Older Age
Myocardial infarction, congestive heart failure, valvular disease, cardiomyopathy
HIV infection
Low potassium level On drugs that lower potassium e.g. Diuretics
Low prothrombin level
On medications that inhibit Cytochrome p450 3A4: • HIV antivirals e.g. indinavir • Antifungals e.g., Fluconazole, ketoconazole • Calcium channel blockers e.g., Diltiazem, verapamil • Antimicrobials e.g., Norfloxacin • Antidepressants e.g., Fluvoxamine • Contraceptives e.g., Mifepristone • Grapefruit juice • Alcohol use • Cocaine use
Family or past history of long QT syndrome
History of syncope or sudden cardiac death in the family
On medications that prolong QTc: • Cardiac medications e.g., amiodarone, sotalol • Antipsychotics e.g., chlorpromazine, haloperidol, pimozide, thioridazine • Antibiotics e.g., clarithromycin, erythromycin • Anti-nausea drugs e.g., domperidone
Methadone doses above 120 mg

References

1. Goldfrank L, Weisman RS, Errick JK, *et al.* A dosing nomogram for continuous infusion intravenous naloxone. *Ann Emerg Med.* 1986; **15(5):** 566-70.
2. LoVecchio F, Pizon A, Riley B, *et al.* Onset of symptoms after methadone overdose. *Am J Emerg Med.* 2007; **25(1):** 57-9.
3. Caplehorn JR, Drummer OH. Fatal methadone toxicity: signs and circumstances, and the role of benzodiazepines. *Aust N Z J Public Health*. 2002; **26(4):** 358-62; discussion 362-3.
4. http://www.atforum.com/SiteRoot/pages/addiction_resources/Drug_Interactions.pdf). www.hivclinic.ca/man/drugs_interact.html
5. http://www.cpso.on.ca/policies/guidelines/default.aspx?id=1984
6. Abramson DW, Quinn DK, Stern TA. Methadone-Associated QTc Prolongation: A Case Report and Review of the Literature. *Prim Care Companion J Clinic Psychiatric* 2008; **10(6):** 470-476

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