THERAPEUTICS

Maintenance drugs to treat opioid dependence

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Philip Routledge, professor of clinical pharmacology, Cardiff University. To suggest a topic for this series, please email us at practice@bmj.com.

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- Newer drugs for focal epilepsy in adults (*BMJ* 2012;344:e345)

A 39 year old woman started injecting heroin when she was 18 but soon found she could not control her drug intake or her life in general. At age 30, she sought help and did well with methadone treatment, taking no illicit drugs for three years. However, she then relapsed to heroin use and spent a year in prison, where she continued to inject heroin. After being released, she went to a residential rehabilitation centre. Subsequently in the community her general practitioner started her on buprenorphine. Her life became more stable. She did well with buprenorphine treatment for a few years but restarted injecting heroin after stopping buprenorphine. She restarted buprenorphine and now takes no non-prescribed medication. She works as a waitress and lives with her non-drug using partner.

What is opioid dependence?

This article is intended for practitioners who occasionally manage patients with opioid dependence. Methadone, a mu opioid agonist, and buprenorphine, a partial agonist, are the main drug treatments for dependence on opioids (which include heroin, morphine, and oxycodone, as well as the other pharmaceutical opioids[1 2]) for detoxification, maintenance, and ultimately abstinence. Treatment with maintenance goals is referred to as opioid substitution treatment or opioid agonist pharmacotherapy.[3] Such treatment is reserved for patients with clearly established opioid dependence and prolonged daily opioid use (by either smoking or injecting). In some countries the combination of buprenorphine and naloxone is preferred (and is now becoming available as a film taken sublingually). Prescription heroin, known in the United Kingdom as heroin assisted treatment or injectable opiate treatment, is used in some countries but is not discussed in this article.[4-6] Naltrexone blocks the effects of heroin on the mu receptor,[2] but oral naltrexone treatment has had low adherence and high discontinuity rates.[7 8] Use of naltrexone in the form of implants and extended release injection is currently in the research and development phase[9] and is outside the scope of this paper.

How well do methadone and buprenorphine work?

More than 30 randomised controlled trials report moderately strong evidence of efficacy as measured by reduction in non-prescribed opioid use, reduction in mortality, and retention in treatment.[3 10-13] A Cochrane review found that retention in treatment was lower for buprenorphine than for methadone when flexible doses were used (relative risk 0.85; 95% confidence interval 0.73 to 0.98).[11] This translates to a number needed to treat of 9.62, indicating that for every nine people treated with methadone one additional person will be retained in treatment than would be the case with buprenorphine. Despite the breadth of published evidence (summarised in the table), opioid substitution treatment remains controversial, with some strongly polarised views on the priority of outcomes ranging from stable maintenance to stable abstinence from all drugs.

Effectiveness of methadone or buprenorphine, based on systematic reviews and large scale cohort studies

	Event rate (intervention) (%)	Event rate (comparison) (%)	Effect size (95% CI)	Number needed to treat	Strength of evidence (based on GRADE system)*
Methadone maintenance (intervention) *v* no treatment (comparison)					
Retention[12]	173/254 (68)	63/251 (25)	3.053 (1.75 to 5.35)†	2.17	High
Use of opiates[12]	28/104 (27)	110/126 (873)	0.323 (0.23 to 0.44)†	1.59	Moderate
Criminal behaviour[12]	5/178 (3)	18/185 (10)	0.393 (0.12 to 1.25)†	4	Low
Overdose mortality[3]	70/37516 (0.2)	416/32454 (1.3)	0.17 (0.05 to 0.63)†		Moderate
Buprenorphine 16 mg (treatment) *v* buprenorphine 1 mg (comparison)[11]					
Retention	110/181 (61)	74/185 (40)	1.52 (1.23 to 1.88)†	4.76	High
Percentage of urine samples positive for morphine			−0.65 (−0.44 to −0.86)‡		High
Flexible buprenorphine (intervention) *v* flexible methadone (comparison)[11]					
Retention	281/531 (53)	340/537 (63)	0.85 (0.73 to 0.98)†	9.62	High
Percentage of urine samples positive for morphine			−0.12 (−0.26 to 0.02)‡		
Self reported heroin use			−0.12 (−0.31 to 0.07)‡		

*The GRADE (Grading of Recommendations Assessment, Development and Evaluation) system classifies strength of evidence as high when further research is very unlikely to change confidence in the estimate of effect; moderate when further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate; low when further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate; and very low when any estimate of effect is very uncertain.
†Relative risk.
‡Standardised mean difference.

Data on mortality from randomised controlled trials are weak because of the small size of the studies, but larger scale cohort studies report a significant reduction in mortality for methadone maintenance compared with no treatment (relative risk 0.17; 0.05 to 0.63).[3] A wide range of clinical guidelines including those from the World Health Organization,[3] National Institute for Health and Clinical Excellence (NICE)[14] and more than 20 multilingual national guidelines,[1 15] support the use of methadone and buprenorphine. Although treatment often includes psychosocial assistance (as in the case scenario above), the nature, extent, and benefits of adjuvant psychosocial assistance is uncertain.[3 16] Nevertheless, psychosocial assistance is generally demanded as a necessary component of the overall treatment programme and considered an indicator of quality. When cessation of medication is unplanned, most individuals return to heroin use and crime.[17]

How safe are methadone and buprenorphine?

A recent analysis of data from the UK General Practice Research Database calculated standardised mortality ratios of 5.3 (95% confidence interval 4.0 to 6.8) for patients "on treatment" (taking opiate substitution treatment) and 10.9 (9.0 to 13.1) for patients "off treatment" (not taking it).[18] Other studies have also found high rates of deaths from overdose after cessation of opiate substitution treatment, and significantly lower annual death rates for those in continuous opiate substitution treatment (1.6%) compared with death rates in the year after patients stopped treatment (8.2%).[17] This substantial difference in mortality risk[3 17-19] makes both methadone and buprenorphine important agents for reducing mortality in a treatment population.

Methadone

The first two weeks after methadone is started has been reported as being associated with a greater risk of death (crude mortality rate 1.7 per 100 person years compared with 1.3 per 100 person years for those off treatment),[18] but once patients are stabilised on methadone the mortality risk drops significantly (to 1.32 per 100 person years in weeks 3 and 4 of treatment, and to 0.61 per 100 person years for the rest of time on treatment).[1 18 20]

A dose related prolongation of the QT interval and sleep apnoea is reported with methadone, but cardiac events are infrequently reported.[21] Individuals with a history of cardiac disease and those taking very high doses of methadone should have electrocardiography.

Buprenorphine

Buprenorphine is less of a depressant than methadone and is thought to cause a lower mortality risk from overdose at the start of treatment, and fewer QT interval changes, but insufficient data are available for quantifying the difference.

What are the precautions?

Starting treatment

Cautious dose initiation with methadone is essential. Supervision of dispensed medication is needed, together with regular monitoring and review with appropriate adjustment of dosage.[1] If the patient has received treatment recently elsewhere, obtain full information about that treatment from the previous prescribing doctor and/or dispensing pharmacist and check that the patient is not currently receiving medication from elsewhere.[1] The half life of a single first dose of methadone is 12-18 hours, with a mean of 15 hours. With ongoing dosing, the half life of methadone is extended to 13-47 hours with a mean of 24 hours. This prolonged half life contributes to the fact that blood methadone concentrations continue to rise during the first week of daily dosing and fall relatively slowly between doses. Methadone reaches steady state in the body (where drug elimination equals the rate of drug administration) after a period equivalent to 4-5 half lives or 3-10 days. Clinicians should explain clearly that it takes time to complete induction on to methadone and that patients will experience increasing effects from methadone over the first few days of treatment even if the dose is not increased.

Contraindications and use of other drugs

There are no absolute contraindications to methadone or buprenorphine. However, all patients starting on methadone and buprenorphine must be informed of the risk of toxicity and overdose. The risk is highest in the initial period of treatment as stable blood concentrations of methadone are achieved, particularly if heroin or other sedating drugs are used on top of the prescribed medication.

Use of hypnosedative medication with either buprenorphine or methadone is associated with increased risk of overdose and death.[1] When patients are reporting heavy use of alcohol and benzodiazepines and other sedative medication, exercise extreme caution in the early induction and subsequent maintenance phase. In addition, it is essential that the medication is safely stored to avoid children taking it. Supervised dispensing is an important safety strategy, to improve treatment adherence and reduce risk of overdose. Medication supervision will enable monitoring and liaison with the dispensing pharmacist and is strongly encouraged, at least in the early phase of treatment.

Avoid coprescribing of benzodiazepines and tricyclic antidepressants as far as possible. Antiretroviral treatments may interact with methadone, less so with buprenorphine; monitoring is needed, with appropriate dose adjustment.

Severe liver and renal disease

Severe liver and renal disease can result in dose accumulation resulting from slow metabolism and delayed elimination. Consider dose reduction or complete withdrawal when the patient is at risk of hepatic encephalopathy. Monitor liver function enzymes for patients prescribed high doses of buprenorphine. Buprenorphine is contraindicated in the presence of severe liver disease.

Pregnancy and breast feeding

Methadone is safe and effective in terms of consistently better obstetric and perinatal outcomes[22 23] compared with pregnancies in opioid dependent women not receiving opioid substitution treatment. Further studies of buprenorphine in pregnancy are needed, but studies to date indicate its potential usefulness.[24] Opioid substitution treatment can be associated with neonatal abstinence syndrome, but this can be readily managed with withdrawal mangement and supportive care. If required or indicated, medications such

Box 1 | Cost effectiveness of maintenance treatment versus no treatment*

- The incremental cost effectiveness ratio for methadone was £13 700 per QALY (quality adjusted life year) gained; the ratio for buprenorphine was £26 400 per QALY gained.
- Methadone was more cost effective than buprenorphine in all scenarios considered because it is cheaper and yields marginally more QALYs (0.067).

*From cost effectiveness analysis conducted by a NICE panel[13]

as methadone, tincture of opium, morphine, or diazepam can be titrated to withdrawal symptoms.

Side effects

The most critical side effect is overdose toxicity (fatal and non-fatal), which seems to be a higher risk with methadone than with buprenorphine.[1 2] Other side effects of opiates are constipation, sweating, pruritis, loss of libido, and impotence. Patients also complain of severe difficulty in withdrawing from methadone and argue that it results in longer dependence on opioids for them. Clinicians and users state that it is easier to withdraw from buprenorphine, but no robust evidence exists to support this belief.

How cost effective are methadone and buprenorphine?

The NICE and WHO guidelines both considered the comparative cost effectiveness of methadone and buprenorphine.[3 13] Methadone costs less and was more cost effective than buprenorphine,[3] but when other factors (such as patient choice, treatment retention, and the comparatively greater need for supervised dispensing with methadone) were taken into account, NICE concluded that there was a good case for clinicians and patients having access to both medications and for individual clinical considerations to determine which drug to prescribe.[13] Overall, both methadone and buprenorphine are highly cost effective when compared to no treatment. Treatment confers a £5 saving for every £1 spent—that is, savings in costs of criminal justice and health and social care (box 1).[13]

How are methadone and buprenorphine taken and monitored?

Methadone is taken orally, buprenorphine sublingually. In most settings the initial period of medication is under the supervision and observation of a pharmacy or clinic, where instalment prescriptions are written to enable daily or regular supervised dispensing of medication. Methadone

Box 2 | Practical guidance for doctors

Start of treatment (first episode)

- Offer oral methadone or buprenorphine
- The choice of drug should be made jointly by the healthcare professional and the patient (and carer if the patient agrees) after considering the options and taking into consideration the history of previous treatment and previous dose of methadone or buprenorphine
- Clarify that the aim of treatment is to achieve good adherence, stop injecting drug use, and stop use of non-prescribed drugs; where this is not possible, the aim is to reach goals such as reduction in injecting and drug risk behaviour
- Before starting an opioid agonist, offer the patient electrocardiography if physical examination identifies a specific cardiovascular risk or if the patient has a history of cardiovascular disease or a family history of long QT syndrome
- With methadone, begin treatment at the lower end of the licensed dose range and slowly titrate upwards. Doctors need to be aware that methadone 30 mg can be a fatal dose in a non-tolerant individual. Once the patient has been inducted and stabilised, gradually work up to a maximum dose of 60-120 mg over several weeks or months. Be aware that because of the long half life of methadone the cumulative dosing will result in rising blood concentrations by the third day of treatment. When the patient reports high dependence and high dose illicit heroin or methadone use, a clinician may titrate the dose upwards more quickly, but this is best done by a specialist aware of the risk of dose accumulation and potential toxicity. Blood methadone concentrations continue to rise in the first week of treatment, stabilising at 7-10 days. Evidence of intoxication or sedation in the early phase of treatment should result in a reduction in dosage
- With buprenorphine, start with 4 mg and work rapidly up to 8 mg or 16 mg as clinically indicated and in discussion with the patient. Again blood concentrations take 7 to 10 days to stabilise
- Throughout treatment, and especially during titration, monitor and record clinical response, adverse effects, physical health (including changes in weight), and adherence. There is a risk of diversion of prescribed medication and there are dangers to individuals who consume non-prescribed medication if they are not dependent. There are complex legal implications, moral responsibilities, and potential harms around diversion. The nature of the doctor's legal responsibilities differs in different jurisdictions. Doctors need to be aware of the local regulations on prescribing controlled drugs. Treatment monitoring should aim to minimise diversion

Treatment of recurrence

- Be non-judgmental, as in any other condition, and encourage a fresh start and offer oral medication again. Base the choice of drug on the criteria above as well as previous treatment response. Changing from buprenorphine to methadone or vice versa is a useful way to have a fresh start and focus on options for treatment adherence, a treatment plan, and treatment goals

Maintenance treatment

- Listen clearly to and establish agreed treatment goals, both short and long term, and review progress on a quarterly basis. Review long term goals annually
- Advise the patient of the high risk of relapse if he or she discontinues use in the next year
- When withdrawing drugs, do so gradually and monitor for signs and symptoms of relapse
- When the response to agonist treatment is inadequate, review use of alcohol and psychostimulants and the adherence to and dose of medication; consider other causes of non-response, such as comorbid mental health problems

Management of adverse effects

- If the patient reports unwanted effects such as excessive sweating, breakthrough withdrawal symptoms, abdominal discomfort, or other somatic symptoms, consider either increasing the dose for withdrawal symptoms or switching to the alternative medication (methadone or buprenorphine)
- Encourage patients to maintain a healthy diet and to exercise regularly to avoid excessive weight gain
- Encourage reduction or cessation of nicotine and cannabis; assess for the risk of blood borne virus and status (and inform the patient about risks) and possible treatment need. Assess mood and risk of self harm when appropriate

Box 3 | Tips for patients*

- There are two main opioid-type agonist drugs that are effective and available: methadone and buprenorphine. Neither is perfect, but both can help you stay away from heroin. Having a very clear focus on what you expect the drug to do will help. Both these drugs are opioids and you will be dependent on them. Users' views vary widely on the difficulty involved in coming off methadone, and some users state that they would prefer to come off buprenorphine. It's possible to work down to a low dose of methadone and switch to buprenorphine, but many prefer to stick to the medication they are familiar with
- You need to be aware that, like heroin, these drugs when taken in larger doses can seriously suppress breathing and consciousness and can result in overdose and death. Mixing these tablets with heroin and other opiates can also be dangerous and result in serious consequences
- You will do much better if you are on a higher dose (methadone >80 mg/day; buprenorphine 12 mg/day); for a longer period (at least 18 months), think carefully about stopping treatment before doing so; plan your discharge from treatment and decrease the dose very slowly (more than three months)
- If you are still using heroin, ask if your dose of your opioid can be increased
- This is a good time to try and sort out other problems in your life and engage in education, training, or to get work
- If you are provided with doses of methadone or buprenorphine, keep these in a child proof container in a safe place
- If you do inject drugs, make sure that you use a sterile needle and syringe every time
- Have a test for HIV and hepatitis C virus, and arrange vaccination for hepatitis A and B
- Try to stop smoking—if you need help to do this, phone a helpline, visit a website, or see a counsellor (phone Smokefree (0800 022 4 332) or go to http://smokefree.nhs.uk/; in Australia go to www.quitnow.gov.au/)
- Take care of your health, including dental health and gum disease, to ensure that dental disease that is caused by drug use is kept to a minimum
- The length of treatment is variable. Some people who do very well on methadone and buprenorphine are advised to stay on it indefinitely; others, after a period of stability, want to get off it. Some do so successfully, but many others find they have to restart the medication. It is much better to restart the medication than to return to street heroin use and crime
- It is important that your GP or treatment specialist monitors your physical health as well as your mental health while you are receiving treatment
- You can take methadone in liquid form usually once a day. Some people prefer to take it twice daily—this is usually more practical once you are able to take medication home from the pharmacy
- Buprenorphine (and buprenorphine with naloxone) comes as a small tablet that is inserted under the tongue and dissolves; in some countries it is available as a small film strip, which dissolves under the tongue more quickly than the tablet
- Alcohol and illicit drugs can interfere with the effects of the opioid drugs and can make you more likely to lose control of your substance consumption and consume a range of other drugs
- It's important that you make your treatment preference clear to your doctor and also that you make clear what you hope to get out of the treatment and that you have a chance to review whether you are getting to where you want to get to and that other options for change are considered if you feel that you have got stuck and stopped making progress

*Based on advice from the Reading Users Forum (a forum in Reading for drug and alcohol users)

is taken once daily. Most patients take buprenorphine daily, but some take it every other day or very occasionally three times a week. Methadone requires low dose induction, with a maximum initial dose of 30-40 mg (but note that 30 mg is a potentially fatal dose in a non-tolerant individual); maintenance doses range from 60 mg to 120 mg, built up over time. Buprenorphine doses can be increased at a faster rate but may precipitate opioid withdrawal if heroin has been recently consumed. Box 2 provides practical guidance to doctors for prescribing these agents, and box 3 outlines tips for patients.

Supervised urine collection and analysis can show if the patient is using non-prescribed drugs but this adds to costs. The evidence for cost effectiveness of urine testing is weak.

How do methadone and buprenorphine compare with other drugs and each other?

Compared with buprenorphine, methadone is associated with considerable stigma but is less expensive, achieves higher rates of retention, and has been used more extensively and evaluated more frequently.[3 10-12 19] The increased risk of death when starting methadone can be reduced by adherence to induction guidelines.

Some people find both methadone and buprenorphine unacceptable, and use of dihydrocodeine[25] has been tried off licence with reasonable success. Studies of slow release oral morphine have also reported positive outcomes.[26] Heroin assisted treatment can also be considered for patients who find methadone and buprenorphine unacceptable but is generally reserved for patients who are severely dependent and have been refractory to all other treatments on many previous occasions.[4 27] When heroin is not available, other medications, such as hydromorphone, have been studied for such patients.[28] Methadone and buprenorphine are now available in 73 countries, and the evidence for effectiveness and cost effectiveness is far stronger than for all other treatments for severe heroin dependence.

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ANSWERS TO ENDGAMES, p 50 For long answers go to the Education channel on bmj.com

STATISTICAL QUESTION
Crossover trials

Statement *b* best describes the allocation of participants to treatment.

ANATOMY QUIZ **Bones of the hand II**

A: Hamate
B: Lunate
C: Ulnar styloid
D: Capitate
E: Scaphoid

CASE REPORT
Anaemia and unexplained abdominal pain: looking for a lead

1 These results suggest disruption of the haem synthetic pathway at the level of ALA dehydrase.
2 Lead poisoning.
3 Ingestion of traditional drugs with a high lead content.
4 Identification and removal of the source of lead exposure and treatment with chelating agents.