

Practice

Practice controversy

Methadone tolerance testing in drug misusers

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Asking drug misusers the dose they need for methadone maintenance might seem like an invitation to exaggerate, but experience in one practice suggests that it could improve uptake of treatment without compromising safety

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The use of methadone maintenance to treat opioid addiction was controversial when it was introduced in 1965. It has since gained respectability, with evidence showing that it reduces mortality,¹⁻³ criminal activity,⁴ and transmission of bloodborne viruses⁵; improves physical and psychological wellbeing⁴; and facilitates social reintegration.¹ The mortality of illicit drug users is around 20 times that of their peers,⁶ but methadone maintenance treatment reduces the risk of death by over 75%.²⁻³ However, mortality is higher at the start of treatment.⁷⁻⁸

After reports of methadone toxicity in the first two weeks of treatment highlighted the dangers of excessive starting doses in patients without “demonstrated tolerance,”⁷ many countries issued guidelines that limited starting doses for maintenance treatment to 20-40 mg (see bmj.com).⁹ Yet such low doses do not eliminate mortality associated with starting treatment⁸⁻¹⁰ and may not be sufficient to alleviate withdrawal symptoms until the next dose, thus discouraging addicts from entering or staying on treatment. We believe that testing methadone tolerance, which uses an initial dose that approximates the patient's usual opioid intake, provides a better solution. We describe the rationale behind this method, our experience of its effectiveness, and our safeguards against methadone toxicity.

Risk of undertreatment

Unless planning to detoxify, patients with high tolerance need high doses of methadone. If the substituted amount of methadone is less than their opiate habit, addicts will usually top up with illicit heroin, methadone, or benzodiazepines until they have reached adequate maintenance doses. Postmortem studies of deaths during methadone induction have detected the presence of alcohol, benzodiazepines, and other substances in most cases.²⁻⁷⁻⁸⁻¹⁰ Thus, these deaths may result not from the methadone itself but from misuse of these other drugs. Undertreatment with methadone could, paradoxically, increase the risk of toxicity.

A systematic review of randomised controlled trials has shown that higher methadone doses (60-100



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Injecting drug users may be more likely to accept tolerance testing

mg/day) are more effective than doses under 60 mg in both retention on maintenance treatment and reduction of illicit drug use.¹¹ It is difficult to randomise for methadone doses greater than 100 mg, but evidence exists that outcomes continue to improve with use of higher daily doses in those that need them. For example, a controlled trial found that among 164 patients who were clinically unstable on 100 mg methadone, increasing the dose to 120-780 mg (average 211 mg) daily resulted in better treatment retention and less illicit drug use than among the control group of 101 randomly selected patients on daily doses of 10-100 mg (average 69 mg) at the same centre.¹²

UK national guidelines recommend doses 60-120 mg as most effective but do not give a maximum dose.¹³ Yet nearly 75% of British primary care methadone prescriptions are for doses less than 40 mg.¹⁴ In a primary care survey of 204 methadone maintenance patients the drop-out rate was 50% after one year of treatment.¹⁵ Thirty seven per cent of those who dropped out left because of underdosage or rigidity of the appointment systems, while 33% were expelled for misdemeanours such as urine samples testing positive for illicit drugs. Highly tolerant patients most in need of treatment are thus least likely to receive it.



Details of guidelines are on bmj.com

Testing methadone tolerance

At Lisson Grove Health Centre (an inner city general practice with 7500 patients), we try to overcome this problem by testing methadone tolerance to tailor the patient's starting dose to their usual opioid intake. Our philosophy is to facilitate treatment for opioid addiction as much as possible. Thus, we offer same day appointments, and any opioid addict entitled to NHS care and living in our catchment area can enter treatment promptly. Our assessment procedure follows national guidelines (see bmj.com).¹³ If we consider methadone maintenance appropriate and the patient consents, we test tolerance at the first opportunity.

Careful questioning of patients about the drugs used and the existence of true opiate withdrawal is vital. The dose given is based on the patient's experience with street or prescribed methadone—that is, the dose a patient says will “hold” him or her. In patients who have not previously taken methadone, we avoid using doses over 40 mg for tolerance testing. However, illicit methadone is so common in the United Kingdom that we rarely see addicts who have not used it. Addicts often use benzodiazepines intermittently to treat withdrawal symptoms. We explain that if the methadone dose is right, they should not need benzodiazepines.

A local pharmacy supervises the first dose of methadone at an arranged time. The patient is instructed to return immediately to our practice to be observed for signs of toxicity. Box 1 details the steps we take to reduce the risks of tolerance testing. Naloxone is available in case of intoxication but has never been needed in the 10 years we have used this approach. Patients are informed of the risks and signs of methadone toxicity. If there are no signs of intoxication, this dose of methadone is continued under the daily supervision of the pharmacist and a review is arranged within a few days. We do not allow patients to take drugs away until illicit use is reduced as shown by opiate negative urine samples, self report, and other data. One of our patients remains on supervised consumption after 12 years for this reason.

Box 2 gives the outcomes of our experience of testing for methadone tolerance. We believe this procedure may improve treatment uptake even for highly tolerant or high risk addicts who failed to engage with other services. For instance, we know of no primary care methadone programme engaging similarly high proportions of homeless people, a group with high risk behaviours¹⁶ and twice the risk of dropping out of treatment.¹⁵ Injecting drug users are another high risk group. They form a higher proportion of our patients (82%) than the average (68%) for services in our area (Westminster).¹⁷

Toxicity during methadone induction

Like all long acting drugs, methadone can accumulate and cause delayed toxicity. High starting doses of methadone and dose increases during titration, as well as low tolerance and drug interactions, have been thought to cause toxicity during the first two weeks of treatment.^{7 8}

Accumulation

The great individual variability in the metabolism of methadone means that caution is needed when starting treatment in patients who have not been regular methadone users. However, the numbers of deaths during induction after methadone maintenance was introduced in the UK were similar to those reported when non-accumulating diamorphine was routinely prescribed for addiction, suggesting that accumulation may not be the over-riding factor in these deaths.^{18 19} Furthermore, although accumulation might be expected to be greater at high doses, a recent study showed that the magnitude of accumulation actually drops at higher doses.²⁰

After death, plasma methadone concentrations can increase up to fourfold because the drug is lipophilic and redistributes from fatty tissue.²¹ Thus, it is impossible to estimate the true concentration of methadone just before death. We believe methadone accumulation can be considered to have caused death only if the person was not tolerant to the *in vivo* concentration. Thus patients who show no sign of intoxication during tolerance testing would have needed much higher doses to become drowsy, dysarthric, or ataxic and higher doses still to develop respiratory depression. Because we do not expect the patient to be in withdrawal when we perform the test we know that the patient can tolerate opiate levels above the test dose.

Box 1: Steps to reduce risks of tolerance testing

- Ensure a safe and effective test dose:
 - Make it clear to the patient that the test dose is based on mutual trust
 - Explain the pros and cons of methadone treatment and tolerance testing orally and in writing
 - Ask the patient to sign an informed consent form that confirms the quantity of recent methadone use
- Explain the risk of overdose:
 - Explain that peak blood levels will rise daily during the first week of treatment
 - Inform patients that risk of overdose is increased on days 3-6 after starting methadone but that most deaths have occurred in people who used other drugs or alcohol simultaneously
 - Explain that, for this reason, you do not prescribe sedatives during the induction phase and reassure them that sleep should normalise with an adequate dose of methadone
- Educate patients about signs of toxicity:
 - Inform patients that most methadone deaths have occurred during sleep but that patients were clearly intoxicated to their friends, family, and presumably themselves for many hours before
 - Advise carers that unusually loud snoring is a common sign of overdose and to clear the airway and call an ambulance if they find the patient unrousable
- Make arrangements for tolerance testing by phoning the pharmacist in front of the patient:
 - Be precise about timing the test dose, which the pharmacist should watch the patient swallow
 - Instruct the patient to return to the practice immediately after this to be observed for signs of intoxication (particularly drowsiness, dysarthria, and ataxia)
- Check the patient's contact details and mobile phone at first appointment
- Communicate with the previous prescriber if appropriate
- Review the patient within days of the first dose. If there are any concerns, time the consultation 2-4 hours after the methadone dose on day 3
- Communicate with pharmacist about compliance
- Do not issue a prescription for a period beyond the review date

Box 2: Experience of testing methadone tolerance

From 1 January 1995 to 1 January 2005, we conducted 141 methadone tolerance tests among 121 patients on our methadone programme.

Patient characteristics

84 men, 37 women

40% (14/35) of women were sex workers

Age at presentation: 16-51 years (average 26 years, median 34 years)

Social history: 90% unemployed, 74% had no fixed abode, and 73% had been imprisoned for drug related offences

Drug use: 87% were multiple drug users, 82% injecting drug users, and 80% had received previous addiction treatment

Comorbidities included hepatitis C infection (61%), psychiatric illness (23%), and HIV infection (5%)

Methadone tolerance testing

30 patients had more than one methadone tolerance test

Test doses were 20-150 mg (average 63 mg, median 70 mg); 23 patients received doses of at least 100 mg

No patient showed evidence of methadone intoxication during the observation period

Outcome

Average duration of care was 36 months

76 were still registered at the end of this period

40 patients left our care: 27 of whom had planned transfers to other services for geographical reasons; three were imprisoned; only 10 left without further arrangements. Assuming that prisoners continue some form of treatment, our drop-out rate was 10/121 or 8%

No methadone related deaths occurred. Three patients died from natural causes and two had heroin related deaths (one after leaving prison where he had been detoxified and the other after discharge from a psychiatric unit where methadone maintenance had been discontinued)

Drug interactions

Given the difficulties in interpreting postmortem results, it is hard to determine the exact role of methadone in people who have taken more than one drug. A survey of 50 drug related deaths in the first week of methadone maintenance found evidence of multiple drug use in 46 cases (92%), and only four of the 50 had had methadone prescribed at doses above those recommended by (contemporary) guidelines.¹⁰ A study of 35 consecutive methadone related deaths showed the presence of several other drugs in all but

Summary points

Most patients starting methadone maintenance are put on low doses that may not prevent withdrawal because of fears of toxicity

Most deaths at start of maintenance occur in patients who have taken multiple drugs and could be due to undertreatment

Methadone tolerance testing allows the starting dose to be tailored to a patient's requirements

The approach seems to increase uptake among addicts at highest risk

Appropriate safeguards can minimise the risks of accumulation

one case; toxic levels of other drugs were present in 12 (33%) of these cases, while death was found to be due to gunshot wounds and carbon monoxide poisoning respectively in two cases with the highest methadone levels.²²

Caplehorn found other drugs present in the bodies of seven out of 10 people who died during methadone induction; tolerance to opiates was doubted in five cases, and nine showed clear signs of intoxication the day before death.⁸ It is reasonable to conclude that some of these deaths could have been avoided by testing methadone tolerance and briefing patients and their carers about signs and risks of accumulation. Caplehorn recommends daily review during the induction phase,⁸ but our impression is that such reviews usually take place before patients take the methadone. Review some hours after ingestion would be more relevant.

Safeguards in testing methadone tolerance

We matched the starting dose of methadone to the patient's tolerance and, despite using starting doses of up to 150 mg of methadone, did not encounter any methadone related toxicity or deaths in our case series. However, accumulation of this long acting drug and its delayed toxicity remain potential hazards, and we take safeguards against this (box 1). Our audit cannot quantify the safety of testing methadone tolerance compared with other induction methods. Induction deaths are expected in 0.2% at most,⁸ and our numbers are thus too small. We therefore recommend a rigorous trial to compare methadone tolerance testing with conventional induction methods.

Our experience is that patients do not undertake methadone tolerance testing for a dose they have not used before and for which they cannot predict the effect. Our patients know they will be observed and that naloxone will be used if needed. In practice, patients' judgment of their dose requirement has proved accurate, and patients do not like to risk showing themselves intoxicated by the dose they ask for. Addicts who request high doses are likely to be those who neuradapt most readily and are thus least likely to succumb to accumulation. Interestingly, despite our use of starting doses that the General Medical Council might well consider irresponsible, the only drug related deaths in our series occurred after methadone had been discontinued.

Contributors and sources: AB has a special interest in treating substance misusers and has been trying to optimise treatment access, choice, uptake, and outcome. CF has worked on addiction since 1966 and evaluated many drug treatment clinics for the Department of Health. She was chief of demand reduction for the UN Drug Control Programme from 1990 to 1998. AB is guarantor and wrote the current version of the article. CF wrote the original paragraph on homelessness, did statistical analysis, and contributed to the literature search. John Caplehorn provided details and suggestions for this article and Emma Richardson collected data on homelessness.

Competing interests: AB is a good friend of Colin Brewer, whom the GMC recently found guilty of irresponsible prescribing practices including methadone tolerance testing.

1 Grönbladh L, Ohlund LS, Gunne LM. Mortality in heroin addiction: impact of methadone treatment. *Acta Psychiatr Scand* 1990;82:223-7.

- 2 Caplehorn JR, Dalton MS, Haldar F, Petrenas AM, Nisbet JG. Methadone maintenance and addicts' risk of fatal heroin overdose. *Subst Use Misuse* 1996;31:177-96.
- 3 Van Ameijden EJ, Langendam MW, Coutinho RA. Dose-effect relationship between overdose mortality and prescribed methadone dosage in low-threshold maintenance programs. *Addict Behav* 1999;24:559-63.
- 4 Keen J, Oliver P, Rowse G, Mathers N. Does methadone maintenance treatment based on the new national guidelines work in a primary care setting? *Br J Gen Pract* 2003;53:461-7.
- 5 Sullivan LE, Metzger D, Fadula PJ, Fiellin D. Decreasing international HIV transmission: the role of expanding access to opioid agonist therapies for injecting drug users. *Addiction* 2005;100:150-8.
- 6 European Monitoring Centre for Drugs and Drug Addiction. Overall mortality among opiate users. *Annual report 2004: the state of the drugs problem in the European Union and Norway*. <http://ar2004.emcdda.eu.int/en/page079-en.html> (accessed 23 Oct 2006).
- 7 Drummer OH, Opekin K, Syrjanen M, Corder SM. Methadone toxicity causing death in ten subjects starting on a methadone maintenance programme. *Am J Forensic Med Pathol* 1992;13:346-50.
- 8 Caplehorn JRM. Deaths in the first two weeks of maintenance treatment in NSW in 1994: identifying cases of iatrogenic methadone toxicity. *Drug Alcohol Rev* 1998;17:9-17.
- 9 Leavitt SB. *Methadone dosing and safety in treatment of opioid addiction*. Mundelein, IL: Addiction Treatment Forum, 2003.
- 10 Zador D, Sunjic S. Deaths in methadone maintenance treatment in New South Wales, Australia 1990-1995. *Addiction* 2000;95:77-84.
- 11 Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. *Cochrane Database Syst Rev* 2003;(3):CD0022008.
- 12 Maxwell S, Shinderman M. Optimising response to methadone maintenance treatment: use of higher dose methadone. *J Psychoactive Drugs* 1999;31:95-102.
- 13 Department of Health, the Scottish Office Department of Health, Welsh Office, Department of Health and Social Services Northern Ireland. *Drug misuse and dependence—guidelines on clinical management*. London: Stationery Office, 1999.
- 14 Strang J, Sheridan J, Hunt C, Kerr B, Gerada C, Pringle M. The prescribing of methadone and other opioids to addicts: national survey of GPs in England and Wales. *Br J Gen Pract* 2005;55:444-51.
- 15 Hutchinson SJ, Taylor A, Gruer L, Barr C, Mills C, Elliott L, et al. One-year follow-up of opiate injectors treated with oral methadone in a GP-centred programme. *Addiction* 2000;95:1055-68.
- 16 Klee H, Morris J. Factors that characterise street injectors. *Addiction* 1995;90:837-41.
- 17 National Drug Treatment Monitoring System. *Injecting status of individuals in contact with structured drug treatment agencies by drug action team area of residence and strategic health authority of residence 2003-4*. www.nta.nhs.uk/programme/national/docs/NDTMS_2003_04_Injecting.xls (accessed 26 Oct 2006).
- 18 Ghodse AH, Sheehan M, Taylor C, Edwards G. Deaths of drug addicts in the United Kingdom 1967-81. *BMJ* 1985;290:425-7.
- 19 Oppenheimer E, Torbutt C, Taylor C, Andrew T. Death and survival in a cohort of heroin addicts from London clinics: a 22 year follow-up study. *Addiction* 1994;89:1299-1308.
- 20 Greenwald MK. Early impact of methadone induction for heroin dependence: differential effects of two dose sequences in a randomized controlled study. *Exp Clin Psychopharmacol* 2006;14:52-6.
- 21 Drummer OH. Post mortem toxicology of drugs of abuse. *Forensic Science Int* 2004;142:101-13.
- 22 Pirnay S, Borron SW, Giudicelli CP, Tourneau J, Baud FJ, Ricordel I. A critical review of the causes of death among post-mortem toxicological investigations: analysis of 34 buprenorphine-associated and 35 methadone-associated deaths. *Addiction* 2004;98:978-88.

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When I use a word ...

The matter with "issue"

The word issue comes from the Latin word exitus (Italian uscita, French issue), from the supine form exitum of the verb exire, literally "to go out." Even in Latin, exire and exitus had several meanings; in English, issue has too many.

There are three forms—the substantive (noun), verb transitive, and verb intransitive. We can deal summarily with the verb forms. To issue [something] means to send it out—an edict, stamp, coin, banknote, report, threat, ultimatum; other meanings are obsolete or rare and all reflect the primary meaning. This form has also spawned an indirect passive form (*BMJ* 2002;325:387), to be issued with [something]—at one time much reviled but now an accepted part of the language. To issue [intransitive] means to go out or (viewed from the other side) to come out; none of the nuanced variations of meaning that issue from this primary meaning is much used today.

However, the substantive poses a serious issue, I mean problem. The *Oxford English Dictionary* (2nd edition) gives 39 separate meanings, listed under seven headings and 16 subheadings. Three extra entries in the second volume of the *Additions Series* (1993) make it 42. Here is a classification that partly tames the multitude, or at least as many meanings as you need; I omit the obsolete and rare.

The issue actual—The action of exiting, a sortie.

The issue rhetorical—Everything about a discussion or argument ("the whole issue").

The issue medical—A discharge ("matter," when purulent, hence my title).

The issue legal—A child, breed, race; proceedings or profits; the point in question (also in the phrases "at issue," "to take issue [with]," "to make an issue [of]").

The issue military—Rations, rum, uniform, a revolver.

The issue financial—Bills of exchange, shares, coins, banknotes, stamps.

The issue bibliographical—Newspapers, magazines, journals; an item lent by a library.

The issue political/managerial—And here's where the trouble starts:

- The management should deal with this issue [matter]
- I intend to reopen the issue [discussion]
- Do not confuse the issue [the fundamental question]
- Every departmental issue [conflict] has been avoided
- We must consider the issues [details] of any plan
- We have brought the work to a successful issue [conclusion]
- We must debate the managerial issues [principles]
- We have enough care issues [questions] to worry about
- We have enough bed issues [problems] to worry about
- We have enough prescribing issues [errors] to worry about
- Does all this create issues [difficulties]?

The managerial use is seductive because the speaker uses the word to mean almost anything, cloaking uncertainty and ambiguity. Harvey Marcovitch (former editor of *Archives of Disease in Childhood*) tells me that in one case, when atheists objected to a document that contained numerous references that implied God's existence, each instance of the word God was replaced by the phrase "issues surrounding God." A perfect illustration. Then there is the public relations concept of "issue management," in which otherwise unacceptable policies are sold to the public by astute advertising or spin.

This is not a new problem. I have adapted many of my examples from *What a Word!* by A P Herbert, a compilation, first published in 1935, of material that originally appeared in *Punch*.

This little word cannot bear so many quasi-meanings. As Ernest Gowers succinctly asserted in *The Complete Plain Words* (1954), "[issue] has a very wide range of proper meanings as a noun, and should not be made to do any more work—the work, for instance, of subject, topic, consideration, and dispute." Quite so. Expunge it—then we won't have any issues.

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We invite readers to contribute their own favourite examples of the (mis)use of "issue" as Rapid responses.