Supervised dosing with a long-acting opioid medication in the management of opioid dependence.

Trials challenge the need for the widely accepted policy of making opioid-dependent patients take their methadone or other opioid substitutes at the clinic or pharmacy, but 'no difference' findings may be due to the limitations of the research.

SUMMARY International guidelines recommend opioid substitution treatment, such as methadone and buprenorphine maintenance, as first-line medication treatments for opioid dependence. A negative aspect of these treatments is that medication can be diverted through sale on the black market and unsanctioned use. Daily supervised administration of medications (taking the drugs at a clinic or pharmacy under the supervision of a clinician) has the advantage of reducing the risk of diversion and may promote therapeutic engagement, potentially enhancing psychosocial aspects of the treatment, but costs more and restricts the patient more than dispensing medications to be taken away from the clinic or pharmacy ('off-site' consumption).

The featured review aimed to compare the effectiveness of opioid substitution treatment with supervised consumption relative to dispensing medication for off-site consumption. Analysts searched for relevant reports published in any language. Eligible studies may have randomly allocated patients to supervised versus non-supervised consumption, formed a comparison group in some other way, or followed-up patients in routine treatment, comparing those being prescribed methadone or buprenorphine on a supervised versus unsupervised basis.

Six studies were found, four of which had randomly allocated patients to supervised consumption versus some other administration procedure, and two of which had followed up routinely-treated patients being supervised versus not supervised. Altogether 7999 participants were involved. For different outcomes, the quality of the evidence was low to very low. Where appropriate, outcomes from different studies were combined in a meta-analysis.

Main findings
Combined findings generated no significant differences in the time supervised versus unsupervised patients were retained in treatment. Additionally, data at 12 months from a study not included in the combined results (because patients were not randomly allocated) also found no difference in retention.

There were no significant differences in the proportion of patients who had used non-prescribed opioids at the end of the supervised versus unsupervised period (67% when supervised, 60% unsupervised) nor in the proportion who admitted to letting someone else have their medication (5% supervised, 2% unsupervised), though both findings were from the same single study (below), and the quality of the evidence was considered poor.
The study was all about supervised consumption of methadone in a pharmacy. There were also no significant differences in the incidence of adverse effects or severity of dependence. Data on deaths were reported in two studies. One was a US randomised trial which reported two deaths in the supervised group (considered unrelated to the treatment), while an Irish study of routine treatment found all-cause mortality lower when patients were regularly supervised, but this difference became non-significant when adjusted for other factors related to the death rate.

No studies reported on pain symptoms, drug craving, aberrant opioid-related behaviours, days of unsanctioned opioid use, or overdoses.

The authors’ conclusions
Take-home medication strategies are attractive to treatment services due to lower costs, and place less restrictions on patients. Due to the low quality of the evidence for the outcomes assessed for this review, there remains uncertainty about the effects of supervised versus unsupervised dosing, and in particular whether lack of supervision is associated with more diversion and unsanctioned use of medications. Strategies for individual patients should be decided on a case-by-case basis, taking into account the characteristics of patients, including social factors such as employment status and relationships.

Findings
Recommendations on supervised consumption in UK clinical guidelines are relatively (eg, in comparison with the USA and Australia) relaxed about this safeguard against diversion, though in line with World Health Organization advice. Leaving the decision to guided clinical discretion, they advise that in most cases it will be appropriate for new patients to be required to take their daily doses under the direct supervision of a professional for a period of time to allow monitoring of progress and an ongoing risk assessment. In some cases, assessment will suggest supervision is needed for an extended period, in other cases, only for a short period. Duration of supervision should, say UK guidelines, depend on assessed clinical need, not be set in an “arbitrary” manner – in other words, not determined according to some time limit or other criterion which bears no necessary relation to individual circumstances.

The featured review seems to support such an approach, finding no evidence-based reasons to stipulate blanket supervision. It also found no conclusive argument against supervision, and in particular no evidence that it led to early dropout from treatment, a risky event for the patient and for the community. However, trials of the kind included in the review could only assess impacts on the patients being supervised or not supervised, yet the main function of extended supervision is not to safeguard the patients, but other people. Above all, supervising consumption is intended to prevent methadone being sold on the illicit market or otherwise ‘diverted’ to other people, possibly extending addiction in the population and resulting in fatal overdoses. A UK population-wide study implied that supervision does indeed prevent methadone-related deaths overall, not just among the patients, but could not say whether it prevented opioid-related deaths in general, including those due to heroin. Also, overly intrusive anti-diversion measures could generate deaths by deterring treatment entry and, despite the findings of the review, possibly also retention. These arguments are detailed below.

Does supervision save lives?
As well as missing deaths due to diversion, even in respect of impacts on the patients, randomised trials tend to sample too few patients and to be too short-term to be able to register significant differences in a rare event such as death during treatment. They may also sift their participants such that adverse events are less frequent than in routine practice. These limitations did not apply to a study in Ireland (one of the routine-treatment studies included in the featured review) of patients prescribed methadone in primary care between 2004 and 2010. Its implications were, however, complicated by a limitation of non-randomised studies – that there may not have been a level playing field between the approaches being compared.

Rather than being randomly allocated, records of patients in routine treatment were analysed, including times when they were known to be on a supervised consumption regimen. Over the six-year study period, 6983 patients were documented sufficiently to be included in the analysis. Typically they
were followed up for about four years and four months. Unexpectedly, regular supervised consumption was not associated with fewer deaths – all the more remarkable because the comparison was not between periods during treatment when consumption was supervised versus not supervised, but between treatment featuring regular supervision and other periods both in and out of treatment. The effect would have been to load on to the non-supervised periods the risks of being out of treatment altogether, yet still supervision was not associated with a reduced death rate. A feasible explanation is that supervision was imposed at particularly risky periods or on patients not complying with treatment, and that their heightened risk of death was reduced by supervision, but not significantly below the level of patients at lower risk to begin with.

Instead of following up individual patients, a different kind of study examined national trends in methadone-related overdoses in Scotland and England, including both patients and other people to whom medication may have been diverted. It found that declines between 1995 and 2004 in the rate of methadone overdose deaths per dose of prescribed methadone coincided with more widespread adoption of supervised consumption as routine practice. The conclusion was that supervision does reduce mortality due to this cause, but the study was unable to determine whether the advent of supervised consumption meant each opiate user in or out of treatment had become less likely to avoid overdose death – not just those involving methadone, but also heroin and other opioids. These findings relate to the adoption of supervision as a treatment policy, and do not necessarily support the inflexible application of that policy to individual patients.

**Balancing the pros and cons**

Limitation of the study cited immediately above to methadone-related overdoses is important, because supervised consumption and other anti-diversion measures might under certain conditions reduce methadone-related deaths, but only at the expense of increasing deaths involving illicitly obtained opiates or due to other causes. On the plus side is the fact that preventing diversion also prevents it creating a breach in the medication 'shield' which helps block a wholesale return to illegal opioid use and injecting, possibly with contaminated equipment. Some forms of diversion also threaten patient welfare through the injection of unsuitable preparations such as oral methadone, and through heightened risk of overdose. Diversion also risks the lives of other people who acquire the medication, particularly those not as used to ('tolerant' to) opioids as the patient. Especially when illicitly manufactured supplies are scarce, diverted medications can fuel the spread of dependent opioid use. In a climate of antipathy to maintenance prescribing of drugs like methadone, the consequences of poorly controlled diversion can threaten a particular service or the modality as a whole; effective anti-diversion measures may be essential simply to keep the service running so patients can benefit from its life-saving potential.

On the minus side, an overly restrictive anti-diversion regimen can deter access to treatment, costing lives which might otherwise have been saved. Especially in respect of buprenorphine, a relatively safe medication, untreated heroin addiction is seen as generally a greater threat to health than diversion and misuse. Even when controls are relatively lax, making maintenance treatment widely available can save more lives than it costs. Patients generally dislike supervised consumption and the need for frequent pharmacy or clinic visits. "Greater flexibility", "Fewer rules" and "Reduced number of months of supervised dosing" were the top regimen changes which opiate-addicted patients being prescribed medications in the UK told researchers would make it easier for them to stay in treatment. In the same study, nearly half the opiate users not in treatment said what kept them out was the requirement for daily supervised consumption. Anti-diversion controls may be time-consuming and costly, using up resources which could have been used to extend treatment to more patients. Diverted medications are often taken by people already dependent on opioids who would otherwise be using illicitly produced drugs. Many take this medication for purposes similar to those promoted by treatment services – to maintain stability, prevent or manage withdrawal, and reduce use of illegally produced substances. These consumers risk death due to overdose and other causes, but perhaps less so than if they had used illicit products instead. Anti-diversion measures can also prevent patients self-managing their treatment. Patients who store doses 'for a rainy day', split them so they can take half later, or inject non-injectable preparations, may be safer retained in imperfect treatment than deterred from treatment anti-diversion tactics. Where illicit manufactured supplies are plentiful, a small amount of leakage from treatment services will have little impact on the extent of opioid addiction.

**Main UK trial**

With its tradition of 'take-home' doses, the UK has contributed several important studies. The largest UK randomised trial assessed 627 patients prescribed methadone or buprenorphine at...
English clinics, but excluded 236 because they were judged to need (202) or not be suitable for supervised consumption. In the end, 293 patients were included in the trial, randomly allocated to supervised consumption for the then-recommended three months (normally followed by unsupervised dosing), or to a comparison group supervised only for a week to four weeks while doses were adjusted and patients stabilised.

In the event, another 60 patients did not receive their intended supervision regimen. In effect, the study narrowed down to one of supervised versus unsupervised consumption among the minority of patients who, it was judged, could safely and feasibly be allocated to either, reducing the chances of finding one option preferable to the other.

There were no significant differences in retention in treatment (though this favoured patients allocated to shorter supervision) or in illegal drug use or drinking, nor were there any differences on quality of life measures. There were, however, significant differences in self-reported crime, which since the start of the trial had become less common and less frequent among patients allocated only to initial supervision compared to those allocated to be supervised throughout this period. Very few patients (5% supervised, 2% unsupervised) said they had let another person have their drug.

Reanalysing the data in terms of the regimen patients actually received produced similar findings, except that the gap in retention became greater, and supervised patients left significantly sooner. Also, at the 12-week follow-up a significantly higher proportion of patients (73% versus 52%) allocated or moved to three-month supervision had used heroin. These findings might, however, have been partly due to the reasons why patients changed from their intended regimens in the first place, rather than due to the regimens themselves.

For more on supervised consumption of methadone or buprenorphine in the treatment of opioid addiction search the Effectiveness Bank database.

Thanks for their comments on this entry in draft to James Bell of King's College London in England. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

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