FINDINGS **Your selected document**

▶ Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK.

Cornish R., Macleod J., Strang J. et al.

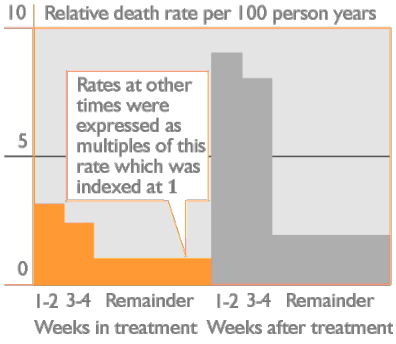
British Medical Journal: 2010, 341:c5475.

This British study concluded that it takes extended opiate substitute prescribing to realise the treatment's life-saving potential. The implication is that the current push to get people off methadone sooner could cost lives.

SUMMARY This study sought to quantify the degree to which prescribing opiate substitutes has extended the lives of opiate-dependent primary care patients in Britain, whether deaths were more common at different stages of the treatment process, on different opiate substitutes, or among certain types of patients, and to probe whether longer treatment was more effective.

It drew on a large database of records of about 3.5 million patients attending over 460 UK general practices, affording a reasonably representative sample of primary care patients. With minor exceptions, the researchers analysed records of all patients with a diagnosis of substance misuse who had been prescribed methadone or buprenorphine between 1990 and 2005 inclusive, tracking their fate through prescription records until the end of this period or until they left the practice. Patients who left treatment were tracked until a year after the expiry of their last prescription. The sample numbered 5577 patients largely aged in their 20s and 30s, of whom 7 in 10 were men. 88% had been prescribed methadone with or without other substitute medications (including for many dihydrocodeine) and 25% buprenorphine. Typically, during the 16 years analysed by the study patients had been prescribed opiate substitutes once or twice for just over two months each time. Some had however been in treatment much longer, extending the average episode to nearly eight months. On buprenorphine durations averaged just under six months, over two months less than on methadone. A quarter of treatment episodes included at least one daily dose at or above the recommended maintenance thresholds of 60mg methadone, 12mg buprenorphine, or 600mg dihydrocodeine.

In all 178 patients died while being tracked by the study. Of these, 62 were still in treatment, defined as up to the expiry of the last prescription they received during that treatment episode. Death rates were standardised as equivalent to the number of deaths which at the observed rates would have been seen during a year among 100 patients ('per 100 person years'). To level the playing field, they were then adjusted for any differences between the age or sex breakdowns of the patients, the dates they were in or out of treatment, and the degree to which the number of non-substitute medications they were prescribed indicated that they suffered from other complaints – a rudimentary 'comorbidity' index. After these adjustments, the death rate while out of treatment was over twice as high (229%) as while in treatment. Compared to the general population of the same sex and age range, while in treatment patients were about five times more likely to die, but while out of treatment, nearly 11 times more likely.



While death rates were much lower in than out of treatment, the relative gains varied substantially across a treatment episode and its aftermath ▶ *chart*. Safest of all was being in treatment after the first four weeks, when patients have had time to stabilise their lives and their dose of substitute medication. Compared to this period, most risky of all was the four weeks after leaving treatment, when the death rate was 8–9 times higher. Beyond these four weeks, being out of treatment was much less risky, but still nearly twice as risky as the 'stabilised' treatment period. The death rate was also elevated during the first four weeks of treatment, when doctors and patients may have been feeling their way towards a safe but effective dose, and some patients may not yet have adjusted to life without heroin. Compared to later in treatment, the death rate during this induction period was 2–3 times higher. Fortunately its brevity meant this elevation was overshadowed by later treatment, so that overall being in treatment was safer than not being treatment.

The analysis of whether the duration of treatment affected risk attributed deaths in the four weeks after treatment to the treatment period. This in-treatment death rate was then compared to the rate which would have been found without treatment, assumed to be the rate from four weeks after leaving treatment. On this assumption, around nine months was the 'break even' point. Shorter treatment durations were associated with similar or progressively worse death rates than without treatment and a less than 50-50 chance that lives were saved. Longer durations were associated with lower death rates than without treatment, and at least a 50-50 chance that treatment saved lives, rising to a better than 8 in 10 chance after around a year and to virtual certainty after another four months, a level sustained at least up to nearly two years of treatment.

Also of interest was what death rates were *not* significantly related to. Given its safer pharmacological profile, surprisingly deaths were not significantly less frequent on buprenorphine than on methadone, even during the relatively risky induction period when buprenorphine's advantages should have been most evident. Overall death rates were lower after 1990–1994, but then did not improve over the next 12 years. Whether the treatment episode featured at least one dose at or above recommended levels made no substantial difference to overall death rates. One in ten methadone treatments but nearly half on buprenorphine ended with a presumed attempt to ease treatment exit by gradually reducing doses to very low levels, but this made no significant difference to the excess mortality in the four weeks after leaving treatment.

The authors' conclusions

Compared to the general population, opiate users in this study had a substantially higher risk of death. The overall risk of death during opiate substitution treatment was lower than the risk of death out of treatment and this net benefit increased with the duration of treatment. However, relative to their remaining time in treatment, in the first month patients were at two to three times higher risk of death; in the month after leaving treatment, the risk was eight to nine times higher. There was no strong evidence that these findings differed whether methadone or buprenorphine was prescribed, whether doses at least matched recommended thresholds, or whether treatment exit seems to have been planned for by tapering doses.

Informed speculations can be made about reasons for the findings. Respiratory depression is the main cause of opiate overdose deaths, and this risk is heightened when the body's 'tolerance' to opiates – the degree to which it has become used to high doses –

has faded due to reduced use. This is commonly the case after the end of treatment, making the patient vulnerable to overdose until tolerance has been re-established. This together with the fact that relapse is common after treatment could explain the high post-treatment death rate. Induction on to opiate substitution treatment, especially with methadone, also poses risks if the initial dose is too high or if patients continue to use non-prescribed opiates, and the change to methadone may be distressing. Closer supervision of induction alongside more effective post-treatment anti-relapse strategies should mitigate these risks. Otherwise the heightened risk of death at either end of treratment may negate any protective effect, unless treatment is prolonged. In the featured study, the average duration of treatment was 34 weeks, not necessarily associated with a net reduction in deaths.

COMMENTARY At a time when the the national policy emphasis in the UK is on limiting the duration of substitute prescribing, this study suggests relatively extended treatment is required to realise the treatment's life-saving potential. This is partly because the short but risky induction and treatment exit periods are counter-balanced by the relatively safe period in between, when patients and dose have presumably been maximally stabilised. The longer this period of relative stability, the greater the net benefit. Fed in to a simulation model for the UK, this data led to the estimate that shortening an average nine-month treatment to six would cause 10% more deaths while extending it to 12 months would lead to a 5% decrease.

The featured study's finding derive from the treatment system as implemented up to 2006 by general practitioners. Findings might be different – and there might be less need for extended treatment to save lives – if induction were handled better, there were more robust support structures for patients leaving treatment, or the caseload mix changed to patients (perhaps intercepted earlier in their addiction careers) more compliant with treatment from the start and then able to securely overcome their dependence in a shorter time. But until 2006 and probably even now, it seems that British GPs were unable to prevent elevated risk at the two ends of methadone/buprenorphine prescribing programmes. Whether specialist hospital-based addiction treatment clinics were doing any better is not known.

That being in an opiate substitute prescribing programme is associated with half the risk of death of not being in such a programme mirrors international findings which amalgamate to a similar ratio. But the featured study leaves open the question of just what the comparator was; some former patients might have moved to other treatments, others will not have been in treatment at all. Nor does it mean that dependent opiate users who did *not* opt for substitute prescribing would – had they changed this minds – have experienced the same benefits. What it does suggest is that opiate users considered suitable for substitute prescribing, and who seek or at least accept this treatment, are likely to live longer if this treatment is made available than if it is not, and that as recently provided in the UK, the longer they are in these programmes, the greater the life expectancy dividend. Even this conclusion might be challenged if the kind of people with (at least at that time of their lives) the kind of resources and supports which enable them to stick with treatment would in any event have been at lower risk than less promising patients. That may account for part of the apparent life-saving dividend, but from other studies (1 2 3 4) we know it is not the whole story; substitute prescribing does have a real life-saving impact.

The greatly elevated death rate in the immediate post-treatment period is a surprise though not unprecedented ▸ details below. It highlights the need for post-treatment monitoring and support, though this may be difficult to engineer for patients who simply drop out. This need is likely to become even greater given the emphasis in the current drug strategy on enabling drug users in treatment to progress to becoming drug free rather than remaining for many years on substitute medication.

Once again the study demonstrated that most opiate maintenance patients in Britain are prescribed doses below recommended levels. The finding that recommended doses did not save more lives must be seen in the context of the fact that just one instance was all it took to categorise a treatment episode as featuring recommended doses; patients consistently prescribed these doses may well have been better protected from overdose death. Given its safer pharmacological profile, another apparent surprise is that deaths were not significantly fewer on buprenorphine than on methadone, even during the induction period, when buprenorphine's safety advantages should have been most evident. However, the numbers were very small. In Australia, of the 121 deaths during the first two weeks of opiate prescribing programmes, just one occurred on buprenorphine and the remainder on methadone, creating the expected statistically significant advantage for buprenorphine.

While substitute prescribing generally extends the lives of its patients, the featured study confirms that this is not inevitably the case. Other reports have highlighted deaths among non-patients who have obtained methadone on the illicit market. Whether lives are on balance saved depends on achieving the right balance between access and control, flexibility and regulation. Get this right, and methadone and buprenorphine programmes make the greatest known contribution to reducing opiate-related deaths. Get this wrong, and deaths due to diverted medication, among patients unable to access the programme, who continue to use illegal drugs due to inadequate doses, whose induction on to methadone has not been sufficiently well monitored, or who have been forced out or deterred by expense, onerous requirements, or unrealistic expectations of compliance and progress, can all become a concern.

Why was leaving treatment so risky?

An elevated death rate during induction is expected and in line with prior research (for example, 1 2 3). The worrying surprise in the study was the greatly elevated death rate immediately after leaving treatment. Just these four weeks saw 41 of the 178 deaths – nearly a quarter – recorded by a study which on average tracked patients for over three years. Fatal overdose seems the only conceivable primary cause of an elevation of this size over such a short period. Why this might have happened among patients who left treatment after dose reductions is clear: like patients exiting detoxification or who stop taking opiate-blocking medications, they would probably have lost most of their tolerance to opiate-type drugs, leaving them vulnerable to overdose if (as many would have done) they relapsed to illegal heroin use. But they were the minority. All we know of the remaining patients is that they died shortly after their last prescription for methadone or buprenorphine expired. Had they immediately relapsed to heroin, they should have retained the protection of the tolerance maintained by the prescribing. The assumption must be that some had to, or tried to, do without opiates for a short time, but within the next few days relapsed to illegal opiate use when their tolerance would have faded.

Though most clearly shown in the featured study, such an effect is not unknown in other countries. In Australia the death rate in the first two weeks after leaving (mainly) methadone treatment was about three times that during the stabilised treatment period, and might have been higher still except that the first six days after leaving were considered part of the treatment period. Overdoses were the main cause of death. An Italian study (previously analysed by Findings) found that methadone maintenance patients and former patients were at substantially lower risk of fatal overdose than patients from other treatment modalities and that, if less so than during treatment, they remained at lower risk after leaving. But in this study too, the overdose death rate after leaving methadone maintenance was much higher than during treatment, probably due to deaths shortly after patients had dropped out. Echoing the featured study, the researchers commented that in any modality, short treatments might fail to save lives because risks were concentrated at the start and immediately after the end, counterbalanced by the time in between. Contrary to these studies, no post-treatment rise in the death rate was recorded in Amsterdam, possibly because most opiate users there do not inject, so overdose death rates were low overall, and/or because the definition of when treatment ended excluded the first three days, and might also have left the patients with some prescribed methadone still to take.

Thanks for their comments on this entry in draft to the lead researcher Matthew Hickman of Bristol University and to Neil McKeganey of the University of Glasgow. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

Last revised 04 August 2014. First uploaded 08 December 2010

The effectiveness of opioid maintenance treatment in prison settings: a systematic review STUDY 2012
Community loses from failure to offer maintenance prescribing in prisons DOCUMENT 2013
Buprenorphine/naloxone for opioid dependence: clinical practice guideline DOCUMENT 2011
Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence STUDY 2011
Opiate antagonist treatment risks overdose STUDY 2004
A review of opioid dependence treatment: pharmacological and psychosocial interventions to treat opioid addiction REVIEW 2010
Randomized trial of standard methadone treatment compared to initiating methadone without counseling: 12-month findings STUDY 2012
Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence DOCUMENT 2009