DRUG ALCOHOL FINDINGS *Research analysis*

This entry is our analysis of a study considered particularly relevant to improving outcomes from drug or alcohol interventions in the UK. The original study was not published by Findings; click Title to order a copy. Free reprints may be available from the authors – click prepared e-mail. Links to other documents. Hover over for notes. Click to highlight passage referred to. Unfold extra text. The Summary conveys the findings and views expressed in the study. Below is a commentary from Drug and Alcohol Findings.

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▶ Risk of mortality on and off methadone substitution treatment in primary care: a national cohort study.

Cousins G., Boland F., Courtney B. et al.

Addiction: 2015, 111, p. 73–82

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Primary care methadone patients in Ireland were nearly four times more likely to die during periods out of treatment; the first few weeks after leaving were the peak risk period. The study's support for unbroken, long-term treatment runs counter to recent UK government policy.

SUMMARY This study followed up patients prescribed methadone by primary care practices in Ireland to establish whether death rates vary during treatment phases (initiation and cessation) and whether features such as dose and methadone being taken under clinical supervision ('supervised consumption') are associated with death rates.

The context is that numbers in methadone maintenance in Ireland have been increasing, with about a third treated in primary care, but there has been no corresponding decrease in deaths from opioid overdose. Irish guidelines recommend methadone consumption be supervised at least once a week. Supervised consumption is believed to prevent deaths by ensuring patients take their methadone as intended and avoiding it being 'diverted' to other users. Diversion risks patients being under-treated and relapsing to illicit heroin use.

Key points
From summary and commentary

Deaths were tracked among patients in Ireland prescribed methadone in primary care between 2004 and 2010.

Records revealed that patients were nearly four times more likely to die during periods out of treatment, and that the first few weeks after leaving were the peak risk period.

Implications are that efforts should be made to encourage retention and that when patients do leave they should be monitored over at least the first month.

Findings challenge the recent emphasis in the UK on curtailing the duration of opioid substitute prescribing programmes.

Research methods

The featured study was based on cross-referencing official records kept nationally in Ireland. It focused on patients prescribed and dispensed methadone in primary care between 1 August 2004 and the end of 2010 identified in a national register of methadone maintenance patients. This register was linked to dispensing records for methadone and all other medications, and to mortality data recorded in a national census of drug-related deaths (deaths recorded on the death certificate as directly attributable to drug use) and deaths among drug users. Patients were followed-up during treatment and (as long as they remained alive) for up to a year after the expiry of their last methadone prescription until the end of 2010.

A patient was defined as still being in treatment if they received their next prescription for methadone within three days of the period covered by their previous prescription, after which UK guidelines say patients should be reassessed before recommencing treatment. Longer gaps were considered time spent out of treatment. Typical doses during each patient's last treatment episode were categorised in relation to the recommended range of 60–120mg daily. Consumption during a given week was assumed to have been supervised if a prescription for the dispensing of a single dose was followed no more than a day later by another for a single dose or for several days. A period of regular supervision was defined as having over half one's prescriptions supervised.

The patients

Over the six-year study period 6983 patients aged 16–65 were prescribed and dispensed methadone and this prescribing was documented sufficiently fully to be included in the analysis. They were followed up for from about a month to over six years, but typically for about four years and four months. Over two-thirds were men and most were aged under 30. Multiple treatment episodes were the norm, though almost 60% of patients had at least one episode lasting a year or more. Almost 60% received doses in the recommended range; nearly all the rest were prescribed lower doses Four in ten had their consumption regularly supervised. Nearly three-quarters had also been prescribed benzodiazepines and nearly half antidepressants.

Main findings

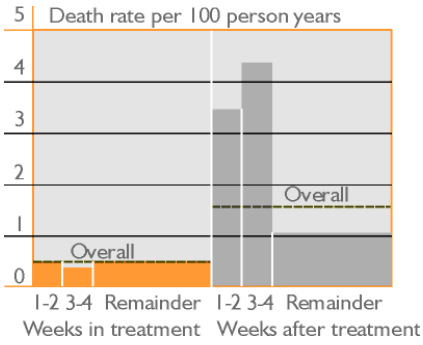
Either during treatment or within a year of leaving, over the six years of the study 213 or 3% of the patients died. Of these, 78 deaths were identified as due to 'poisoning' by drugs, all but a few involving opiate-type drugs and three-quarters benzodiazepines.

With so few drug-related deaths the analysis did not produce statistically significant findings, though some of the relationships between the death rate and other factors were substantial. While in treatment the drug-related death rate was equivalent to 0.24 deaths per 100 patients in treatment for a year, lower than the 0.39 per 100 while people were out of treatment. Lowest of all was the

equivalent drug-related death rate at the start of treatment – just 0.11 in the first two weeks and 0.13

equivalent drug-related death rate at the start of treatment – just 0.11 in the first two weeks and 0.13 in the next two, compared to 0.26 during the remaining time in treatment. The death rate peaked in the weeks after leaving treatment, reaching 0.49 in the first fortnight and 1.19 during the next two weeks. Compared to other times in or out of treatment, drug-related deaths were proportionately slightly fewer while patients were not subject to regular supervised consumption. Deaths were also slightly fewer among patients prescribed less than recommended doses.

The above analysis of the 78 deaths recorded as drug-related was supplemented by one of all 213 deaths, some of which were likely to have been be due to drugtaking even if not recorded as such. With this greater number, some of the relationships between the death rate and other factors were not just substantial, but also statistically significant, so unlikely to have been due to chance variations.



While in treatment the overall death rate was equivalent to an annual toll of 0.51 deaths per 100 patients – after adjusting for other factors, nearly four times lower than the 1.57 during periods out of treatment, a statistically significant difference ▸ chart. Like drug-related deaths, overall deaths were proportionately fewer – but only slightly and non-significantly – during the first weeks than later in treatment, bottoming at a rate of 0.39 during the second fortnight. Also like drug-related deaths, the overall death rate peaked in the weeks after leaving treatment, reaching 3.46 in the first fortnight and 4.38 during the next two weeks. It then fell to 1.07, still significantly greater than (after adjustments, over twice as great) the death rate after the first four weeks in treatment. Contrary to drug-related deaths, compared to other times in or out of treatment, deaths overall were proportionately slightly and non-significantly fewer while patients were subject to regular supervised consumption. As with drug-related deaths, dose bore no substantial or significant relationship to the overall death rate, but this was at its lowest among patients prescribed less than recommended doses.

The analysis for overall deaths was re-run assuming that at least a week's break rather than three days indicated a period out of treatment. This made no material difference to the findings.

The authors' conclusions

Similar to previous studies, during treatment and up to a year after leaving, over a third of deaths among methadone patients in primary care in Ireland were identified as related to drug use, mainly involving opiates and benzodiazepines, and deaths were fewer while patients were in treatment and peaked shortly after leaving.

Unlike previous studies, there was no evidence of an elevated risk of death when starting treatment compared to later treatment periods, nor that regular supervised consumption prevented deaths. Both findings may have been due to inadequate sample size or other factors. Patients in this study may have been transferring between specialist treatment and primary care rather than starting or leaving treatment as such, perhaps accounting for no treatment-entry spike in deaths, and supervised consumption may have been enforced due to the patient's instability, obscuring any restraining influence on the death rate.

Implications are that efforts should be made to encourage retention in treatment in primary care; up to a year after leaving, patients are almost four times as likely to die as when in treatment. When patients do leave, especially over the first month monitoring and follow-up should be considered. Further research is needed to determine the optimal duration and frequency of supervised consumption. Long-term supervision of stable patients may prevent them normalising their lives and lead them (see for example this British randomised trial) to drop out of treatment, even if it also helps prevent illegal drug use during treatment.

The fact that so many patients were also being prescribed benzodiazepines is a concern; these drugs may have contributed to over three-quarters of the drug-related deaths. Such prescribing may reflect a valid need for treatment of anxiety disorders, but may also be a sign of benzodiazepine misuse or of the maintenance treatment of benzodiazepine dependence.

It is important to remember that studies of this kind can only tease out links between variables, not establish that these represent cause and effect; the possibility remains that other factors account for the relationships. However, data linkage studies such as this are an essential means of evaluating the protective effects of treatment. Compared to controlled studies, they allow for larger samples, longer follow-up, and detailed prescribing, monitoring and management information over time.

FINDINGS COMMENTARY This important study adds to evidence that users of heroin or other opiate-type drugs who are considered suitable for substitute prescribing, and who seek or at least accept this treatment, are likely to live longer if it is made available than if it is not. Across relevant studies from around the world, when opioid-dependent adults are in a substitute prescribing programme they are less than half as likely to die as when not in treatment. The longer patients remain in these programmes, the greater the life-expectancy dividend. The first few weeks after leaving are especially fraught as patients relapse to or increase their opiate use while beyond addiction-related medical care.

These conclusions might be challenged if the kind of people with (at least at that time of their lives) the resources and support 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.

Health benefits are one of the main reasons why the World Health Organization has given unequivocal backing to methadone and other forms of long term maintenance treatments as the prime modality for treating dependence on heroin and allied drugs, and why in 2005 it recognised methadone and buprenorphine as "essential medicines".

As detailed below, the implications of the featured study run counter to the preference among senior figures in the UK government for methadone prescribing to be short-term, positions held despite relatively strong evidence of the health and other benefits of extended treatment from a US randomised trial, and from a UK study very similar to the featured study. Evidence is one part of the decision-

trial, and from a UK study very similar to the featured study. Evidence is one part of the decision-making equation, but how strongly that evidence weighs in the balance is a matter of values; as discussed below, some see more deaths as worth the prospect of more revitalised lives. Both the Irish and the UK study found a greatly elevated death rate in the weeks after leaving treatment, the reasons for which are unclear, as is why the Irish study found supervised consumption unrelated to the death rate. Before addressing those issues in more detail, it is important to acknowledge the main limitations of the featured study.

Restricted to patients and to primary care

Though relevant to the survival of people in methadone treatment, the featured study does not add to our knowledge of arguably the more critical question of whether deaths overall of patients *and* non-patients are increased or decreased by widespread methadone maintenance programmes. Other reports have highlighted deaths among non-patients who have obtained methadone on the illicit market. Whether lives are on balance saved depends (1 2) 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.

Another important limitation of the featured study is its restriction to primary care. Patients may not have been typical of the entire Irish caseload in treatment at specialist clinics as well as in primary care, and they may have entered and left primary care not from/to no treatment, but from/to the same treatment conducted in another setting. The most likely transition was from specialist clinics to primary care after patients have been stabilised and dose levels established, possibly accounting for the failure to find that the normally risky first few weeks of methadone treatment (1 2 3 4) was associated with an elevated death rate.

Transition from primary care to a specialist clinic seems less likely. Leaving primary care treatment probably represented leaving treatment altogether, helping explain the greatly elevated death rate. Had the rate in the first four weeks been extended over a year, it would have meant 4 in every 100 former patients dying. Whether the deaths were actually *caused* by leaving treatment cannot be established; perhaps patients left precisely because their lives had become destabilised, or they wanted to return to regular injecting of illegally obtained opiates despite the risks. But other studies in which treatment has been denied or leaving forced on patients (1 2 3 4) suggest that the shield offered by methadone, and perhaps too the associated frequent medical contact, is an active ingredient in avoiding preventable deaths.

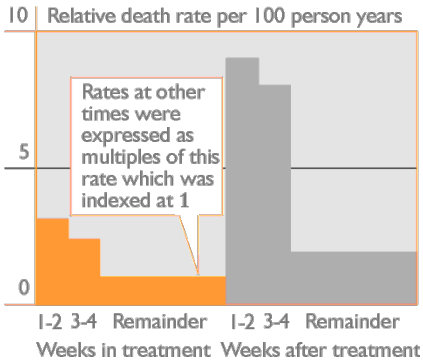
Another limitation of the study is the one-year post-treatment cut off, making it impossible to establish whether the post-treatment death rate trended down as former patients developed lives free of both risky substance use and of addiction treatment.

Corresponding UK study produces results similar to Irish study

A UK study very similar to the featured study also produced similar results. It drew on a large database of records of about 3.5 million patients attending over 460 general practices. 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, 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. Only overall deaths were analysed, not specifically drug-related deaths.

After adjusting for other factors, the death rate while out of treatment was over twice as high (229%) as 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.

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 ▸ chart. Most risky of all was the four weeks after leaving treatment, when the death rate was 8–9 times higher than after the first four weeks of treatment. After patients had survived nearly a month out of treatment, the death rate plummeted, but remained nearly twice as high as during the 'stabilised' treatment period. Unlike the featured study, 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.



Treatment durations longer than nine months were associated with 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.

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.

Fed in to a simulation model for the UK, this data led to the estimate that shortening an average nine-month treatment episode to six would cause 10% more deaths, while extending it to 12 months would lead to a 5% decrease.

Implications contrary to UK government policy

The main implication of both studies – the life-preserving importance of unbroken, long-term treatment – runs directly counter to the attempts of the UK government to gain expert endorsement for setting time limits to opioid substitute prescribing programmes, among which methadone maintenance dominates in the UK as in Ireland. In turn this position reflects the longstanding view among some

dominates in the UK as in Ireland. In turn this position reflects the longstanding view among some senior figures in the current government that rather than being a treatment for addiction, methadone maintenance "perpetuates addiction and dependency".

That view was expressed in July 2007 when in opposition David Cameron's 'New' Conservatives released the fruits of their addictions policy think tank. A similar view was even more trenchantly expressed in Conservative Party policy in the run up to the May 2010 election, which saw methadone maintenance as "drug dependency courtesy of the state", a view which can be seen as translating into addictions treatment policy the Conservatives' determination to reduce dependence on the state in the form of welfare benefits.

Most prominently, in 2012 the same sentiment featured in the coalition government's policy document *Putting Full Recovery First*, presented as "the Government's roadmap for building a new treatment system based on recovery". Signed by the chair of the Inter-Ministerial Group on Drugs and seemingly endorsed by major departments of state including the Cabinet Office, the document promised to bring "an urgent end to the current drift of far too many people into indefinite maintenance, which is a replacement of one dependency with another".

Putting Full Recovery First was a precursor to repeated challenges made to expert advisers to consider and re-consider the evidence for time-limiting methadone prescribing, some of which were recalled in 2013 by Paul Hayes, former head of England's National Treatment Agency for Substance Misuse: "There's still an appetite in bits of government to re-ask the question about time-limited methadone ... which in my time they asked four times and always got the same answer. They keep hoping they'll finally find someone to tell them what they want to hear, but the evidence remains the evidence."

The latest public challenge came in 2014 when the Government asked its official advisers on drug policy on the Advisory Council on the Misuse of Drugs "whether the evidence supports the case for time-limiting opioid substitution therapy". The resulting rejection was the most explicit to surface from an official body. Not only did the Council's report foresee negative health and crime consequences from time limits or otherwise curtailing prescribing, but it turned the tables by arguing that far from being in treatment too long, generally patients in England were there too short a time, and that rather than restricting access to maintenance, access should be widened. In this they echoed the comments of US recovery 'guru' William White for a Scottish report which, as in the UK as a whole, had responded to government concerns over the role of methadone in recovery: "In the US, there are periodic moral panics about the idea of patients being on methadone for prolonged periods – an image that obscures the real problem which is that most patients are not on methadone long enough, eg, high rates of early drop-out, administrative discharge and rapid resumption of opioid addiction."

Revealing the depth of opposition to maintenance in some quarters of government, the Advisory Council's report drew the ire of Iain Duncan Smith, leader of the Department for Work and Pensions, who publicly accused advisers appointed by his own government of "providing cover for perpetuating drug addiction in the UK".

Drug and Alcohol Findings has traced the recent history of opposition to maintenance in Britain in a hot topic entry, which dates the current debate back to the mid-2000s and the then Labour government's concern to contain costs and free up treatment slots by getting patients to the point where they could leave treatment, partially reversing the previous emphasis on retention.

Rare randomised trial finds maintenance cost-effective lifesaver

The Effectiveness Bank's analysis of the Advisory Council's report recounts the "strong" evidence the experts found that "time-limiting opioid substitution therapy would increase the rate of overdose deaths" and have other negative consequences.

Among this corpus, randomised trials have been rare. The most relevant to current British policy was conducted in the 1990s in the USA. It can be seen as having tested a time-limited methadone stabilisation programme acting as a preparation for detoxification – the preferred approach among leading government figures – against something more like extended methadone maintenance. The implications of its findings have been explored in the Effectiveness Bank's Drug Treatment Matrix and in an Effectiveness Bank research analysis. Reports on both the original trial and on a cost-effectiveness analysis are freely available. As detailed below (unfold supplementary text 👁), these showed that compared to post-detoxification patients, patients in the other arm of the trial who were still being maintained used illicit opiates less often, had fewer legal complications, and were at lower risk of blood-borne diseases, translating into an estimated low-cost extension of life. Results also clearly showed methadone's holding power – both its strength as a treatment and the source of its condemnation.

The researchers' verdict was pointed: "[no] support for diverting resources from methadone maintenance to long-term detoxification, no matter how ideologically attractive the notion of a time-limited treatment for opioid abusers." For many the bottom-line argument for maintenance would have been the study's estimate that relative to detoxification, it will have saved lives. That, however, takes us into the domain of values – of what matters most. For some informed UK observers the lifesaving argument is a clincher, but for others, "Leaving the protection of methadone maintenance treatment may increase the risk of death. But it might also be the way to a brand new life beyond your wildest dreams, where you find jobs, homes and friends." The prospect – even the certainty – of more deaths may not convince those who feel a life tied to a methadone clinic to daily swallow the drug in front of staff and submit to observed urine tests, yielding control of significant parts of your life, is not the best of lives. It can be countered that being precipitated back on the streets to fund and obtain illicit heroin is not much of a life either, and much more dangerous. But a proportion of former patients will swim rather than sink – and for some on the banks, the sight of those recovered swimmers leaving methadone and addiction behind is worth the loss of others.

Why was leaving treatment so risky?

In both the Irish and UK studies, the most worrying finding was the greatly elevated death rate immediately after leaving treatment. The UK study was unable to distinguish between 'overdose' deaths known to have been drug-related versus other deaths, but the featured Irish study could. In that study the overdose death rate was relatively high in the four weeks after leaving treatment, but these eight deaths were less than a fifth of all 44 deaths during that period. The implication is that overdoses and other deaths recognised for the purposes of the death certificate as directly due to drug use were not the major reason for the spike in deaths after leaving treatment.

Focusing on the overdose deaths, among patients who left treatment after dose reductions one

Focusing on the overdose deaths, among patients who left treatment after dose reductions one probable mechanism 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 in the UK study, dose-reduction patients were the minority, and in Ireland, many more deaths were not attributed to overdose. It seems possible that treatment-leaving is a marker of a dangerous phase in patients' lives, perhaps being precipitated by escalating illegal drug use, instability, or a greater willingness to take risks.

Similar findings have come from Australia, where the death rate in the first two weeks after leaving (mainly) methadone treatment was found to have been about three times that during the stabilised treatment period. Overdoses were the main cause of death. An Italian study (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. They remained at lower risk after leaving treatment, 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. The researchers commented that in any modality, short treatments might fail to save lives because risks are concentrated at the start and immediately after the end, and are counterbalanced by the time in between.

Contrary to these studies, no post-treatment rise in the death rate was recorded in Amsterdam. Possibly this was 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 patients with some prescribed methadone still to take.

Why no link with supervised consumption?

Regular supervised consumption was not associated with fewer deaths in the featured study – 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.

It seems possible that supervision was imposed at particularly risky periods or on patients not complying with treatment, and that this counterbalanced any restraining effect of supervision on their risks of dying. Also it remains possible that supervision saved the lives of people other than the patients on which the study focused. An important reason for supervising consumption is to prevent methadone being sold on the illicit market or otherwise 'diverted' to people other than the patient for whom it was intended, with possibly fatal consequences in the form of opioid overdose.

A study of methadone overdoses in Scotland and England suggests these concerns are valid and that supervision does have the desired impact. It concluded that declines between 1995 and 2004 in the rate of methadone overdose deaths per dose of prescribed methadone were due to the spread of supervised consumption. However, this study was unable to determine whether each opiate user in or out of treatment had become more or less likely to avoid overdose on opiate-type drugs as a whole – heroin as well as methadone – as a result of the introduction of supervised consumption.

Thanks for their comments on this entry in draft to research author Gráinne Cousins of the School of Pharmacy at the Royal College of Surgeons in Ireland, Dublin, Ireland. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

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