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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Impact of treatment for opioid dependence on fatal drug-related poisoning: a national cohort study in England.

Pierce M., Bird S.M., Hickman M. et al.

Addiction: 2015, 111, p. 298–308.

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Implication of this English study is that to save the lives of people dependent on heroin or similar drugs, they should be engaged and retained in substitute prescribing programmes like methadone maintenance until there is little risk of their relapsing after leaving. Shortly after leaving residential/inpatient settings was the highest risk period.

SUMMARY Among patients treated in England for their dependence on opiate-type drugs like heroin ('opioids'), the featured analysis investigated the relationship between being in or out of different kinds of treatments and whether during that time patients had died of 'overdose' – a fatal drug-related poisoning whether intentional or accidental, and involving any drug. Though this kind of study cannot establish whether treatment has a causal impact on overdoses, it can establish whether the data is at least consistent with there being a protective effect.

Over the four years from April 2005 to March 2009 the study matched anonymised identifiers in two sets of routinely collected records to establish whether people recorded as having received treatment for their dependence on opiate-type drugs had died from drug poisoning. Since deaths may not be registered until some time after the event, records were searched up to the end of September 2011. Just over a fifth of patient records were excluded due to duplicate identifiers, leaving 151,983 patients.

Treatment was categorised as:
• Opioid agonist pharmacotherapy: approaches like methadone maintenance which prescribe opiate-type medications on a long-term basis to substitute for the illegal drugs on which patients were dependent.
• Residential: on the grounds that both are oriented to achieving opioid abstinence, this category combined inpatient detoxification and drug-free residential rehabilitation, which on their own contributed too few 'person years' to be reliably linked to overdose risk.
• Non-residential psychological support provided as a standalone treatment.

Key points
From summary and commentary

In England the study investigated the relationship between 'overdose' deaths and being in or out of different kinds of treatments for opioid dependence.

The least risky period was while in methadone maintenance and allied treatments, the most risky, the four weeks after leaving residential/inpatient care.

The death rate jumped after leaving residential/inpatient or maintenance treatments, but not after leaving non-residential psychological support programmes.

Whether a patient had been recorded as having successfully completed their treatment made little difference to their risk of overdose death shortly after leaving.

Other studies have sometimes found treatment entry and exit to be high risk periods, so for each type of treatment the chances were calculated that someone would die from overdose while out of treatment, in the first four weeks of treatment, during the rest of the treatment period, or in the first four weeks after leaving (and not yet re-entering) treatment. Death rates after having successfully completed treatment (as reported by the service, meaning conclusion of the patient's care plan and mutually agreed discharge) or after having left without successfully completing were compared to other periods.

To help level the playing field, the chances that patients would die were adjusted for sex and age, whether they were recorded as injecting or also problematically using alcohol, benzodiazepines, crack cocaine, or cocaine powder/amphetamines, and whether they had been referred to treatment by the criminal justice system.

Main findings

Being prescribed heroin substitutes such as methadone accounted for 89% of all the time spent in treatment. Each episode of this treatment averaged about 17 months compared to 5–6 months receiving standalone psychological support and 2–3 months in residential or inpatient care.

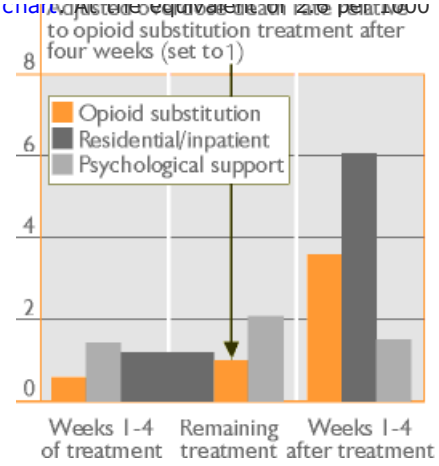
During the four years of the study 1499 patients who during that period had at some time been in treatment for opioid use problems died due to drug-related poisonings, equating over a year to a death rate of 3.4 per 1000 people. Such deaths were more likely among older and male patients and those injecting or also problematically using alcohol or benzodiazepines, but there was no significant or substantial relationship with stimulant use problems. Overall, the least risky period was while in opioid agonist pharmacotherapy, and the most risky (about six times greater) the first four weeks after leaving residential/inpatient care.

Safer being in treatment, especially substitute prescribing

While patients were in treatment the overdose death rate averaged the equivalent of 2.9 per 1000 people over a year, and while not in treatment, 4.5. Adjusted for other factors, there were 1.73 deaths out of treatment for every 1 while in treatment, a statistically significant difference highly unlikely to have occurred by chance. The reduced risk of overdose death while in treatment was much more apparent among men, injectors, and patients who reported problematic drinking, and was only seen among patients not referred to treatment by the criminal justice system.

Risk of overdose death during treatment varied with the type of treatment chart At the equivalent of 2.6 per 1000

Risk of overdose death during treatment varied with the type of treatment ▸ chart. Adjusted equivalent rate per 1000 people over a year, it was least while patients were being prescribed opiate substitutes such as methadone. After adjustments for other factors, it was only slightly and non-significantly greater while in residential or inpatient care. However, at 5.3, the overdose death rate while receiving psychological support was just over twice that in opioid agonist pharmacotherapy.



Compared to not being in treatment at all, after adjusting for other factors patients were nearly half as likely to die (1 death versus 1.92 deaths not in treatment) while being prescribed substitute opioids. The risk-reduction while in residential care was less apparent (1 death versus 1.5 deaths not in treatment), and there was no diminution in risk from being in standalone psychological treatments.

Leaving is a high-risk period

The four weeks after leaving treatment and before (if at all) restarting treatment was a high-risk period, the 2.9 in-treatment overdose death rate increasing to roughly 8. At 4.2 poisoning deaths per 1000 people over a year, risk greatly reduced but remained elevated beyond the first four weeks after leaving and before (if at all) restarting treatment.

The increase in risk after leaving varied with the type of treatment ▸ chart. At the equivalent of nearly 19 overdose deaths per 1000 people over a year, the rate peaked after leaving residential/inpatient care, 69% higher than during the same period after leaving substitute prescribing. Nevertheless, leaving substitute prescribing was also risky – about 3.6 times more risky than the preceding period while being prescribed heroin substitutes. Leaving psychological support programmes was not associated with an elevated risk of overdose death relative to periods receiving these treatments.

Leaving after having successfully completed treatment was only slightly less risky than leaving in other circumstances, and the difference between the two relative to periods in treatment (1.54 and 1.79 times greater deaths rates respectively) was not statistically significant.

Patients referred into treatment by the criminal justice system were an exception to the general rule that being in treatment was associated with a lower risk of overdose death then being out of treatment. For them treatment seemed to make little difference to risk, a result which was not due to the high-risk post-prison period. The seemingly protective effect of being in treatment was on average confined to those treatment episodes (the great majority) which had started in other ways.

The authors' conclusions

The featured study was the largest such study of drug-related poisoning deaths in England to be published to date, drawing on England-wide data from all publicly funded opioid dependence treatment services whether provided by the NHS or by other sectors.

It found that among patients in treatment for opioid dependence at some time from April 2005 to March 2009, risk of death due to drug-related poisoning was greater during periods out of treatment than while in treatment. Consistent with other studies, opioid agonist pharmacotherapy was associated with a strong reduction in drug-related poisoning deaths. Risk increased during the month following discharge from opioid agonist pharmacotherapy or residential/inpatient treatment, and after this remained elevated relative to risk while in treatment. Elevated risk on discharge is consistent with previous studies and probably due to reduced tolerance for opioid drugs, in the case of prescribing programmes, after tapering the dose and cessation of prescribing.

Risk during non-residential psychological support programmes was twice that while in opioid agonist pharmacotherapy, and comparable to the risk when not in treatment – consistent with observations that drug-free treatment is associated with a higher all-cause mortality risk. This is unlikely to be due to any elevated risk in the (very rare) transition from opioid agonist pharmacotherapy to psychological support. Because this was the second most common treatment in the present study, there should be a focus on identifying and reducing overdose risk in patients who receive standalone psychological support for opioid dependence and explicit discussion of this risk with patients.

There was no evidence that completing treatment successfully versus leaving for other reasons was associated with a reduction in risk of overdose death. Though 'successful completion' has face validity as an indicator of clinical effectiveness and has been seen as such in UK policy, it is only a proxy for a good clinical response, not a direct indicator. Possibly too, patients who leave treatment without successfully completing are more likely to retain some protective tolerance to opioid drugs than those who leave after achieving abstinence.

In contrast to previous studies, the featured study found no elevation in risk at the start of substitute prescribing treatments, perhaps because the specialist treatment services responsible for most of the treatment analysed in the study are now more closely following induction guidelines. Nor was risk reduced during treatment among patients referred by the criminal justice system, seemingly consistent with the findings of a large-scale study in England that such referrals were associated with a reduced likelihood of the patient achieving abstinence or reduced use.

It should be stressed that the study was unable to establish causality. Rather than these being wholly caused by the treatments, differences which the study could not adjust for between patients in and out of treatment and in different treatments may have contributed to the findings.

FINDINGS COMMENTARY The clear implication of this study is that to save the lives of patients dependent on heroin or similar drugs, they should be engaged and retained in substitute prescribing programmes like methadone maintenance until there is little risk of their relapsing after leaving – though how that can be established is unclear. By virtue of the study's design, this implication cannot be considered proven fact, and the study did not take into account overdose deaths among *non*-patients to whom prescribed methadone and buprenorphine may have been 'diverted'. But with other research, the weight of the evidence is strongly in favour of treatments like methadone maintenance being the most clearly lifesaving of all common approaches to dependence on opiate-type drugs.

On the debit side, the study also confirmed the high risk of leaving settings like residential or inpatient treatment and prison, which generate abstinence by divorcing the user from their normal environment, and casts further doubt on whether 'successfully completing' treatment is a meaningful indicator of lasting recovery from addiction. These

conclusions are expanded on and substantiated below

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Substitute prescribing least risky across treatment and treatment exit periods

A calculation not made in the featured report is the relative risk of death from each type of treatment while in it, plus the four weeks after leaving and before starting any other treatment. Assuming that rapid post-treatment overdose indicates a deficiency of the treatment – patients must have quickly relapsed for this to have happened – this calculation is as close as the reported data can come to reflecting the overall difference in risks between the different types of treatment.

It can be calculated that the raw figure for deaths during inpatient/residential care plus the four weeks after leaving equated to about 5.81 deaths per 1000 people over a year. The corresponding figure for psychological support was 5.12. At 2.78, for opiate substitute prescribing the corresponding figure approached half that of the other modalities. The raw figure for residential care in particular would need to be adjusted to reflect the relatively high risk of the patients, but still it seems the risk would be around 1.8 times greater than for opiate substitute prescribing.

Safer in specialist services?

The featured study drew its sample mainly from specialist addiction treatment services, but another sampled UK general practices, analysing records of substance misuse patients who had been prescribed methadone or buprenorphine between 1990 and 2005.

In line with the featured study's key finding, after adjusting for factors possibly related to risk of death, the death rate while out of treatment was over twice as high (2.29 deaths for every 1) as while in treatment. But there was also a major difference. At the equivalent of 6.9 deaths per 1000 people over a year, the absolute rate of deaths while in substitute prescribing treatment was far greater than the 2.6 figure registered in the featured study.

One reason would have been the inclusion of Scotland with its much greater rate of drug-related deaths per head of population. Another was that the primary care study analysed all-cause mortality, not just overdose deaths, and spanned a time when supervised consumption had yet to become the norm and when injecting was more common.

More worrying was that the greater rate of deaths among primary care patients was also partly due to an elevated death rate during the first four weeks of treatment – the 'induction' period. At this time the patients were 2–3 times more likely to die over a given time period than later in treatment. In the featured study the reverse was the case, and the first four weeks were actually safer than subsequent treatment, probably because specialist services are more likely than GPs to enforce medically supervised consumption of medication during induction.

Sub-optimal induction does not however fully explain the difference in death rates. Even after the first four weeks, the death rate among the general practice patients was over twice that seen at the specialist clinics. In a sample nearly all of whom were under 50 years of age, and given the escalation in deaths after leaving treatment, this is in turn likely to reflect a greater risk of death specifically due to overdose. Though only a study devoted to this issue could disentangle the causes, it could be that the risk of overdose death was greater in the kind non-specialist treatment provided in the 1990s and early 2000s than in the specialist clinics of the last half the 2000s.

Causality not proven but supported by other studies

That for opioid-dependent drug users, being in a 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. The featured study and its general practice companion study add further weight to this conclusion. However, without randomly allocating patients or a similar way of eliminating differences between them, such studies cannot rule out the possibility that pre-existing differences between patients who enter and leave different treatments accounted for the differences in risk of death, not the treatments themselves. Click for more on this issue.

The kinds of people in the kinds of situations which lead them to enter and stay in substitute prescribing versus other treatments may account for part of the apparent life-saving impact, but from other studies (1 2 3) we know this is not the whole story: substitute prescribing really does save patients' lives. Even among heroin users in Barcelona who had all entered treatment of some kind, the expansion of low threshold methadone maintenance substantially contributed to an increase between 1992 and 1997 in their life expectancy of 21 years. Without the protection afforded by methadone, and even though all the study's subjects had entered specialist treatment of some kind, heroin users were seven times more likely to die.

Some of the most clear-cut data comes from Scandinavia, where resistance to prescribing opiate-type drugs to heroin addicts has allowed the value of these approaches to be more convincingly demonstrated than in countries like the UK. In Norway (1 2) and Sweden, constricted access created quasi-randomised entry to or denial of treatment, stripping away confounding variables like severity of dependence and motivation and exposing the health and life-preserving benefits of the treatment itself.

The single most important study tracked patients admitted to Sweden's national methadone programme before a five-year ban on enrolling new patients. Their fate was compared to that of addicts eligible for the programme, but who did not get in before the ban or had randomly been denied entry. All in this comparison group availed themselves of Sweden's well developed detoxification and drug-free treatment services, yet over on average the next six years, 4 in 10 died. In contrast, over about the same period only around 1 in 8 of the methadone patients had died – bad enough, but far fewer. Deaths in methadone patients were concentrated among those forced to leave rather than leaving voluntarily and with the consent of their doctors, presumably because considered at low risk of relapse – or as the report put it, "rehabilitated". Within seven years, half the expelled patients had died.

Leaving (and succeeding) can be risky

In both the featured study and in the similar British general practice study, the death rate was greatly elevated in the first four weeks after leaving substitute prescribing programmes. Similar findings have emerged in other countries.

The general practice study was able to establish that whether the substitute dose had been tapered before leaving – indicative of a planned end to treatment – made no difference to the risk of death. Across all types of treatment, the featured report also found no protective effect of planned treatment exit. Given its preponderance, these results are likely to mean that at specialist services too, in the English context, leaving opiate substitute prescribing in a planned way does not mean a lower risk of death than leaving in an unplanned way.

But if leaving opioid substitute prescribing treatment is risky, far more so is leaving abstinence-oriented detoxification and rehabilitation programmes. The mechanism almost certainly involves loss of protective tolerance to opioid drugs as

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patients become drug-free in the sheltered environment of an inpatient ward or rehabilitation house. Among these will be many who would otherwise have been unable to achieve abstinence and who resume opioid and other substance use shortly after leaving. Click for more on this issue.

Though of lesser magnitude, the featured study showed that leaving substitute prescribing programmes is also risky. Such findings highlight 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 current UK drug strategies on enabling drug users in treatment to progress to becoming drug-free and leaving rather than remaining in treatment.

Elevated risk among successful completers of some kinds of treatment may help explain why in the featured study leaving after having successfully completed was only slightly less risky than leaving in other circumstances. In their favour, treatment-completers are probably on average more stable and have responded to treatment better than those who do not complete the programme, so may be less likely to quickly relapse. But on the debit side, if they *do* relapse after having tapered their substitute medication or detoxified, they do so at a time when they have lost their protective tolerance. It could be that these influences more or less cancel out, leaving the risk of fatal overdose about the same.

What about the non-patients?

The featured study was concerned only with people treated for opioid dependence at some time during its four-year period, yet 'leakage' or 'diversion' of prescribed opiate-type medications to *non*-patients makes an appreciable contribution to the overall death rate due to opioid overdose. Conceivably, expanding substitute prescribing might cut overdose deaths among the patients, but increase them among non-patients.

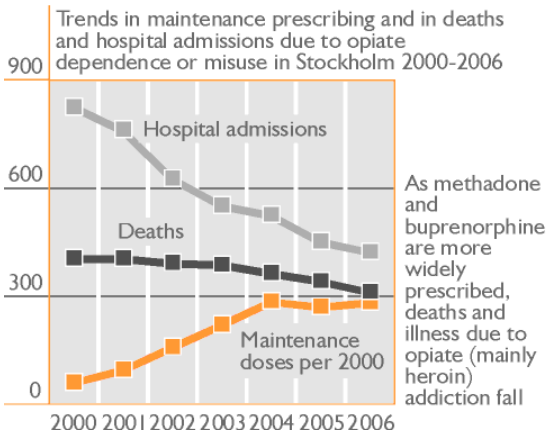
An indication of the scale of this issue, in Scotland in 2014, of the 400 drug-related deaths of people *not* in substitute prescribing programmes, 22% nevertheless had methadone in their bodies at the time of death. Of the 199 deaths in which methadone was not just present, but considered a contributory factor, 40% involved people not known to have been in methadone treatment at the time. Both proportions were substantially down from their recent peaks at 44% and 58% in 2011, but remained indicative of leakage of methadone on to the illicit market and the dangers posed by this leakage.

In England in 2013, 1115 drug misuse deaths had been reported by coroners to a national surveillance scheme. This enriched data source revealed that 37% the 265 deaths in which methadone had been implicated were known to have involved patients being prescribed the drug, meaning that up to 63% involved people who had obtained methadone illegally.

Though leakage still happens, in both England and Scotland the spread of supervised consumption has made methadone services much safer, the death rate per million doses plummeting during the period when supervision became the norm.

We can get closer to estimating the potential for methadone and allied programmes to prevent overdose deaths across patients and non-patients from studies which have assessed deaths in a country or region as a whole. An example comes from Sweden, where as maintenance treatment expanded between 1998 and 2006 there were statistically significant reductions in the number of deaths registered as wholly or partly due to opiate dependence or misuse. This was seen across Sweden as a whole, but more especially in Stockholm, where deaths fell by a third. Autopsy findings showed that deaths where opiates like heroin were found fell significantly, but those in which methadone or buprenorphine were found increased. However, on balance the net tally of drug-related deaths across Sweden fell significantly by about 12% between 2000–02 and 2004–06. There were also significant and/or substantial falls in the number of opiate-dependent or misusing inpatients admitted to hospital, an indicator of trends in ill-health related to opiate use.

Another way to analyse the Swedish figures is to assess how closely year-on-year opiate-related deaths and illness mirrored the expansion in substitute prescribing, indicated by the number of typical maintenance doses sold. Between 2000 and 2006, for both Stockholm (▸ chart; doses converted to per 2000 of the population for clarity) and Sweden as a whole, as prescribing expanded, opiate-related deaths and hospital admissions fell. There was also a strong – but not statistically significant – correlation in the other direction for deaths where methadone or buprenorphine were found in the body: as substitute prescribing expanded, these increased.



In Barcelona too, the increased life-expectancy of heroin users entering treatment between 1992 and 1997 due largely to wider and easier access to methadone maintenance is likely to have had a population-wide impact among all heroin users in the city; the total number of overdose deaths declined over the study period, and as many as three-quarters of the city's heroin users entered treatment, so would have been included in the study's findings.

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