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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▶ The impact of buprenorphine and methadone on mortality: a primary care cohort study in the United Kingdom.

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Buprenorphine may be associated with a lower risk of mortality than methadone among people engaged in opioid substitution treatment – but is the pattern of short treatment duration in the UK preventing maximal impact at a population level?

SUMMARY Opioid substitution treatment is associated with reduced risk of mortality, transmission of HIV and hepatitis C, and drug-related crime, and extended opioid substitution treatment is associated with preventing early deaths. However, there is evidence to suggest an elevated risk of mortality during the first month of opioid substitution treatment and in the month after treatment stops.

Methadone and buprenorphine are effective treatments, and designated by the World Health Organization as essential medicines in the management of opioid dependence. While methadone is a 'full opiate agonist', meaning it produces greater opiate-type effects the higher the dose, buprenorphine is only a 'partial opiate agonist', creating a 'ceiling' of opiate-type effects, limiting the respiratory depression typically responsible for overdose deaths, and attenuating the effect of 'on top' heroin use.

While internationally there is no consensus about which medication to use, in the UK methadone is recommended as the first-line treatment. Qualitative studies in the United States suggest that patient preference for buprenorphine and methadone varies, and may be influenced by peer attitudes, prior treatment experience, and prescription dispensing practices (1 2 3).

Key points
From summary and commentary

This study compared two types of opioid substitution treatment, testing the theory that buprenorphine is associated with a lower risk of mortality than methadone.

An analysis of patient care records found that during treatment at UK primary care practices, buprenorphine was consistently associated with lower rates of overall mortality and drug-related poisoning deaths than methadone.

However, across the population buprenorphine is unlikely to give greater overall protection because of the relatively short duration of treatment.

The featured study tested the theory that buprenorphine would be associated with a lower risk of mortality during opioid substitution treatment than methadone, especially during the first four weeks, and fewer opioid-related poisoning deaths in the population.

Data was collected from the Clinical Practice Research Datalink database, which held the anonymised patient records of 674 primary care practices and more than 11 million patients (7% of the UK population). The researchers selected a cohort of 49,279 patients who received one or more

prescriptions of methadone or buprenorphine between 1 January 1998 and 31 July 2014, and then excluded the 26,324 prescribed buprenorphine or methadone for pain relief, 9,950 patients who received doses below the minimum expected for opioid substitution treatment, as well as patients outside the 15–64 year age range and patients receiving both methadone and buprenorphine within a single period of treatment.

The final cohort comprised 11,033 patients followed-up over 26,546 'treatment episodes' (periods of continuous prescription) and 512,581 prescriptions. The average number of opioid substitution treatment episodes was 2.4, and the average duration of treatment episodes was 14 days, with 17,373 (61%) involving methadone and 9,173 (39%) buprenorphine.

Main findings

Based on prescribing practices, the popularity of buprenorphine increased from less than 20% of treatment episodes between 1998–2000 (83% methadone) to 41% between 2010–2014 (59% methadone).

BUPRENORPHINE VS. METHADONE

Average duration of treatment: 173 vs. 363 days

Drug-related poisoning deaths during the first four weeks (per 100 person–years): 0.30 vs. 1.24

In around 15% of all opioid substitution treatment episodes, and fewer than 10% of those lasting less than two months, there was evidence that doses were being tapered in preparation for discharge from treatment. For 60% of patients their treatment episodes had consisted only of methadone, while 10% had also been prescribed buprenorphine.

The average duration of buprenorphine treatment was less than half that of methadone (173 versus 363 days, or just under six months versus nearly a year), and a lower proportion of buprenorphine treatment episodes met the recommended therapeutic daily dosage – 21% of buprenorphine treatment episodes involving doses of at least 12 mg, and 43% of methadone treatment episodes involving doses of at least 60 mg.

There were 587 deaths (based on the full cohort of 11,033 patients) during opioid substitution treatment plus over the 12 months after leaving without having returned, giving an overall mortality rate equivalent to 1.93 deaths among 100 patients during a year, or 1.93 per 100 'person–years'. During the same time period there were 87 drug-related poisoning deaths (based on a smaller cohort of 5,935 patients in England only), giving a mortality rate of 0.53 deaths per 100 person–years.

After adjusting the analyses for caseload differences and other factors to more accurately estimate the impact of being in or out of the treatments, the lowest risk period was from four weeks into opioid substitution treatment until the end of treatment. Compared to this, during the first four weeks of treatment the death rate was three times higher (the equivalent of 3.11 deaths per 100 person–years, based on raw mortality figures), 10 times higher during the first four weeks after treatment ended (9.54 per 100 person–years), and then nearly three times higher up to a year after leaving (2.19 per 100 person–years). The pattern was similar for drug-poisoning deaths: compared to from the first four weeks after starting treatment until leaving, the mortality rate was nearly twice as high during the first four weeks of treatment (0.89 per 100 person–years), eight times higher in the first four weeks after leaving (1.72 per 100 person–years), and then twice as high up to a year after leaving (0.65 per 100 person–years).

Patients on buprenorphine had a significantly lower overall mortality rate in each time period than patients on methadone, ranging from 25 times lower in the first four weeks of treatment (when there were just two deaths among buprenorphine patients) to about six times lower in the four weeks after leaving, and more than twice as low at other times.

The lower in-treatment death rate on buprenorphine was partly accounted for by there being significantly fewer drug-poisoning deaths both in the first four weeks of treatment (the equivalent of 1.24 deaths among 100 patients during a year for methadone versus 0.30 for buprenorphine) and to a lesser degree also during the remainder of treatment (0.33 per 100 person–years vs. 0.18). However, in contrast to the overall death rate, there was no significant difference in the drug-poisoning mortality rate during the four weeks after leaving methadone versus buprenorphine treatment: 1.61 per 100 person–years vs. 1.89 per 100 person–years respectively. In line with overall mortality, former methadone patients died from drug poisoning at a significantly higher rate in the period between four weeks and 12 months after leaving treatment: 0.83 per 100 person–

years vs. 0.32 per 100 person–years after leaving buprenorphine treatment, equating after adjustments to a fourfold difference.

It was calculated that to be 50% sure of reducing drug-related poisoning deaths by 25% solely by lengthening treatment would require a minimum typical duration of 202 days for buprenorphine and 387 days for methadone.

The authors' conclusions

Compared to methadone, during treatment buprenorphine was consistently associated with lower rates of overall mortality and specifically of drug-related poisoning deaths, including the first four weeks when patients are presumed to be at greatest risk.

There was no evidence of a difference in the risk of drug-related poisoning deaths in the four weeks after treatment ceased, but there was a large and statistically significant difference over the following 11 months to 12 months. This translated into 0.83 deaths among 100 patients during a year for methadone patients versus 0.32 per 100 for buprenorphine patients.

In UK primary care, most patients receive relatively short durations of opioid substitution treatment, and this is particularly the case among patients prescribed buprenorphine. The combination of short average treatment durations and high mortality risk in the period after treatment cessation suggests that in the UK neither buprenorphine nor methadone can impact the number of drug-related poisoning deaths in the population.

Rather than comparing different opioid substitution treatments against each other, further trials are needed that can test how best to optimise opioid substitution treatment alongside other interventions, both to reduce the heightened risk of mortality at the start of treatment and to retain people in treatment long enough to have an effect on the number of drug-related deaths in the population.

FINDINGS COMMENTARY Over the time period of this study, buprenorphine conferred a lower risk of mortality than methadone. However, this added protection was undermined by a shorter time in treatment – less than six months versus 12 months, meaning that the lower risk of drug-related mortality in the year after leaving treatment is to a degree counterbalanced by on average six months less in treatment.

The first four weeks after leaving treatment was observed to be a very high-risk period, the implication being that many patients had not left treatment restored to health and stability. In these four weeks the equivalent of nearly 1 in 10 over a year died, but there was a huge difference between the two medications – about 1 in 7 after leaving methadone compared to just 1 in 43 leaving buprenorphine, equating after adjustments to a six times greater death rate among the former methadone patients. If this was because buprenorphine patients were less likely to quickly relapse, then the same order of differences would have been expected in poisoning deaths, but in fact there was little difference in the drug-poisoning mortality rate. Instead the researchers thought the difference in overall mortality might be due to differences between the type of patients prescribed buprenorphine rather than methadone and/or differences in their situations, raising concerns that other contrasts between the two drugs might also have been contaminated by these factors.

The featured study followed patients prescribed buprenorphine or methadone in real-life circumstances, as opposed to participants randomly assigned. This is important because it removed the artificial research context of prescribing a drug without taking into account the treatment aims of the patient and clinician, such as which drug was more suitable for the patient. However, the treatment aims could have themselves confounded the results – patients on buprenorphine versus methadone could have constituted groups with different motivations. For example, those wanting to divorce themselves from opioids in general (doing without opiate-type effects) are more likely to choose buprenorphine, which is perhaps why treatment duration was found to be shorter and doses lower than methadone. They probably too have a lesser chance of using other drugs and therefore a lesser chance of overdose death, and because of these patient characteristics would have this lesser chance whichever drug was prescribed (4 5).

What about the non-patients?

This study did not involve or make comparisons with dependent opioid users who rejected treatment altogether; it involved participants in the cohort who in the period between four weeks and 12 months after leaving treatment did not re-enter opioid substitution treatment – important, because those who enter treatment (whether successful or not in meeting their aims) may be at a different level of risk to those who never enter treatment.

Another (methodologically-different) study did estimate mortality rate among the never-treated as well as before treatment for those treated, and found treatment strongly associated with lower mortality. It evaluated the impact of treatment by considering what actually happened and what would have happened in the absence of an intervention. In England between April 2008 and March 2011 there was an estimated annual population of about 260,000 opioid misusers (aged 15–64 years), and a population of approximately 160,000 people treated for opioid use each year – 43% receiving opioid medication-assisted treatment such as methadone maintenance, and 38% opioid medication plus a psychosocial intervention. Without any treatment for opioid use problems, the study estimated that there would have been 6,372 opioid-related deaths over the three-year study period. Subtracting the 3,731 deaths which actually occurred led to an estimate that without treatment there would on average have been 880 more opioid-related deaths each year – 71% more than actually happened. This highlighted "an important and underrecognized outcome" from the English substance use treatment system: that being in treatment – and especially for opiate users, being in a substitute prescribing programme – helps prevent overdose deaths.

A study looking at methadone- versus buprenorphine-related deaths among the whole population – as opposed to deaths among treatment patients – found that during the years 2007–2012, 2,366 methadone-related deaths and 52 buprenorphine-related deaths were registered, corresponding to 0.137 methadone-related deaths per 1000 prescriptions of methadone, and just 0.022 for buprenorphine. Based on this, the mortality risk associated with methadone was more than six times that of buprenorphine. This study effectively calculated the chances that each prescription of methadone would be associated with a death involving methadone versus the same metric for buprenorphine, regardless of whether those deaths were of patients being prescribed these drugs. In contrast, the featured study could only account for deaths among (ex)patients, not those among non-patients to whom the medications may have been diverted.

Contrasting findings

While much depends on how it is implemented, internationally and in Britain, being in opiate substitute treatment using methadone or buprenorphine has been associated with a substantially reduced risk of death. Another study of UK primary care buprenorphine and methadone treatment, but from an earlier period (1990 to 2005 rather than 1998 to 2014), also found the risk of death much lower (half as great) while in treatment. However, unlike the featured study it did not find any significant difference in the lifesaving impacts of the two medications as assessed by overall mortality.

Such differences as there were tended to favour methadone. After adjusting for factors including sex, age, date, comorbidity, and dose, per day during treatment there were about 50% more all-cause deaths among patients prescribed buprenorphine versus methadone. At an average treatment episode duration of 245 days for methadone versus 181 days for buprenorphine, on methadone the benefits of being in treatment also lasted longer. Also unlike the featured study, proportionately fewer methadone patients died in the first four weeks after leaving treatment – a substantial, but with small numbers, not statistically significant difference. These findings derive from a time when buprenorphine was more rarely used, perhaps tending to be reserved for higher risk patients.

An Australian study found the expected higher death rate on methadone during the first four weeks of treatment, but after that the death rates were about the same. The study was, however, able to adjust its results only for the age and sex of the patients. 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.

An Effectiveness Bank hot topic on the crisis of overdose deaths in the UK discusses factors that have complicated assessments of the relative death rates involving methadone and buprenorphine (skip to relevant section).

Across the UK there has been concern that methadone – prescribed partly in order to save lives at risk from untreated heroin addiction – is itself implicated in many deaths. Concern has most trenchantly been expressed in Scotland, where in 2017 there were 934 drug-related deaths, of which methadone potentially contributed to deaths in 47% (439). In England in 2013, 1,344 drug misuse deaths were reported by coroners to a national surveillance programme, of which just under a third of the 265 deaths in which methadone was implicated were known to have involved patients being prescribed the drug, meaning that over two-thirds involved people who had obtained methadone illegally. This is a risk less likely to apply to buprenorphine as its properties mean it is harder to divert to the illicit market and less attractive to illegal consumers.

However, evidence of deaths involving methadone is not evidence that deaths would have been prevented if methadone were prescribed less frequently. Without a methadone prescription, these same drug users may have died from a mixture of drugs not including methadone, and other drug users would have died because methadone treatment was denied them.

Another factor perhaps muddying assessments of the relative death rates involving methadone versus buprenorphine both UK-wide and in England is that in suspected drug-related deaths in England, "methadone is routinely tested for, buprenorphine is not. Thus, few buprenorphine-related deaths per 1,000,000 recommended daily doses of buprenorphine may be due to absence of evidence, rather than evidence of a low fatality-rate."

There is a wealth of information in the Effectiveness Bank about buprenorphine and methadone, and their relative safety and effectiveness, for which see this tailored search.

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