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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▶ Fatal opioid poisoning: a counterfactual model to estimate the preventive effect of treatment for opioid use disorder in England.

White M., Burton R., Darke S. et al.

Addiction: 2015, 110, p. 1321–1329

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First robust analysis estimates that between 2008 and 2011, 880 opioid-related 'overdose' deaths were prevented each year by addiction treatment in England, reducing total deaths by over 40%.

SUMMARY A counterfactual model was used to estimate the preventive effect of treatment for problem opioid use on opioid-related deaths in England between April 2008 and March 2011.

[The counterfactual model is a method of evaluating impact, by considering what actually happened (*the factual*) and what would have happened in the absence of the intervention (*the counterfactual*).] It makes the assumption that:

> *If X had not happened, then Y would have happened.*

This was translated into the following question for the study:

> *If no opioid misusing patients had been treated, how many would have died an opioid-related death?*

Answering the question required data on the **prevalence** of opioid use in the general population, the extent of **treatment provision**, and the number of **deaths** related to opioid use.

Prevalence was based on a national estimate of illicit opioid users in England, broken down into three age categories: 15–24, 25–34, and 35–64 years. **Treatment provision** figures were derived from the number of patients who received treatment for problem opioid use from a specialist clinic or primary care team in the National Health Service (NHS) or a non-governmental organisation. This included patients who received a single episode of treatment as well as those who had two or more episodes (either concurrently or consecutively), those who started treatment in the study period, and those who were already enrolled in April 2008. The number of opioid-related **deaths** was based on those documented on the death certificate as involving an opioid drug when the underlying cause was drug abuse or drug dependence, and/or a drug poisoning death involving substances controlled under the Misuse of Drugs Act, where the poisoning or 'overdose' might have been intentional, accidental or not registered as either. All were assumed to be from the population of illicit opioid users counted above.

Key points
From summary and commentary

A model was used to estimate the preventive effect of treatments for problem opioid use, based on data about the prevalence of opioid use in the general population, the extent of treatment provision, and the number of deaths related to opioid use.

This revealed that there would have been 880 extra deaths per year in England between April 2008 and March 2011 if not for treatment.

The analysis highlights "an important and underrecognized outcome" from the English substance use treatment system, and represents one of the largest studies of opioid deaths conducted to date.

Within each year and each age band, the first step was to calculate the time the total population of opioid misusers in England spent in one of three treatment-related states: 'prior to treatment', 'during treatment', and 'after treatment'. Once these were known, it would become possible not just to count the number of deaths while users were in these states, but to express these as rates of deaths over a given time period for a given number of people. This takes account of the fact more deaths would naturally be expected over a longer period and among a greater number of people. For example:

> *There may the same number of deaths (eg, two) while opioid misusers are in treatment as when they are not, making treatment look ineffective at saving lives. But perhaps in any given year, four times as many opioid misusers are in treatment at some time as are not (say 40 vs. 10), and are in treatment for on average nine months of the year. This means that in that year the 40 patients were in treatment for a total of 40x9 months, equating to 30 so-called 'person years' – the product of the number of people and the average time each was in treatment. The 10 non-patients were out of treatment for 10x12 months, equating to 10 person years. To that we can add the 40x3 months the patients also were not in treatment, totalling 20 person years out of treatment compared to 30 person years in treatment. Now it can be seen that over the same period and for a given number of people, deaths were fewer while in treatment. We can express this more clearly by extrapolating the figures to the same number of person years. Two deaths in the 30 person years of treatment equates to 6.67 deaths per 100 person years (the metric used in the featured study). Two deaths in the 20 person years out of treatment equates to 10 deaths per 100 person years. From looking like treatment conferred no protection, we can see that it was associated with a third lower risk than being out of treatment.*

These principles were applied by the study to opioid-related deaths. If someone was 'known' to the researchers because that year they had been recorded as dying and/or being in treatment, the time they spent *in* versus *before* versus *after* treatment could also be known. But what of the tens of thousands of opiate misusers who in a given year are never in treatment and do not die? Estimating their numbers was done by subtracting the number of known opioid misusers from the estimated total population in England (within age band and each year). Their person years out of treatment were added to the 'prior to treatment' time spent by patients who did start treatment at some in the year. Through this step, the researchers were able to parcel out the person years spent by the entire population of opioid misusers in England into 'prior to treatment' (an amalgam of never being in treatment and the time before starting), 'during treatment', and 'after treatment'. They were then in a position to relate the number of deaths while users were in one of these three states to the person years during which these deaths occurred, by calculating a death rate per 100 person years. One remaining complication was how to assign deaths shortly after the last known treatment contact with a patient who dropped out. With prescriptions lasting up to two weeks, they might still in that period effectively have been in treatment, so deaths within this fortnight were assigned to the during treatment state.

To summarise, there were three steps to the counterfactual analysis:
• The time each opioid misuser in England spent in the three treatment-related states was calculated for each year and organised into three age bands, then aggregated across the three years and expressed as a death rate per 100 person years in each state.
• The counterfactual estimate was calculated by applying the death rates in the 'prior to treatment' state to the whole population of opioid misusers within each age band. This simulated a scenario in which across the three years no opioid misuser in England received any treatment.
• Within each age group, subtracting the actual number of opioid-related deaths from this counterfactual equated to an estimate of how many fewer deaths there had been because some of the opioid misusers had been in treatment. Dividing this by three yielded an annual average.

The counterfactual analysis was based on the assumption that (apart from the effects of treatment) the risk of an opioid-related death did not differ among those admitted to treatment in the study period and those not treated, so that comparisons could be made between individuals in the same age group in different treatment states. Furthermore all members of the opioid-using population were assumed to be at risk of an opioid death on each day of the year.

Main findings

There was an estimated annual population of about 260,000 opioid misusers (aged 15–64 years) in England, and a population of approximately 160,000 people treated for opioid use each year, which amounted to 220,665 different people across the study period.

The treatment interventions received by this cohort were: opioid medication-assisted treatment such as methadone maintenance (43%); opioid medication and psychosocial intervention (38%); psychosocial intervention only (10%); in-patient withdrawal management (5%); and drug-free residential rehabilitation (3%). A small minority (3%) were referred for treatment but did not receive or commence it during the study.

There were 3731 opioid deaths between 2008 and 2011: 741 occurred during treatment (0.20 per 100 person years); 2722 prior to treatment (0.77 per 100 person years); and 268 after treatment (0.41 per 100 person years). Of the 3731, 406 (11%) death certificates did not specify the exact opioid, 1968 (59%) specified heroin/morphine, and 1112 specified methadone (33%). Codeine and dihydrocodeine were mentioned in 242 and 243 death certificates. In 2010, there was a notable decline in the proportion in which heroin was specified (49%), and an increase in the proportion in which methadone was specified (41%) compared to the first two years of the study.

Without any treatment for opioid use problems, it was estimated that there would have been 6372 opioid-related deaths over the three-year study period. Subtracting the 3731 deaths which actually occurred led to an estimate that without treatment there would on average have been 880 more opioid-related deaths each year during the study period – 71% more than actually happened. Most of the opioid misusers who would have died without treatment were aged 35–64 (73%), and the smallest number were aged 15–24 (3%).

The authors' conclusions

Bringing together estimates of the prevalence of opioid use in the general population, the extent of treatment provision, and the number of deaths related to opioid use, the counterfactual model generated an estimate that there would have been 880 excess opioid-related deaths each year from April 2008 to March 2011 had it not been for treatment.

The analysis highlights "an important and underrecognized outcome" from the English substance use treatment system, and represents one of the largest studies of opioid deaths conducted to date, using data about the entire treatment population, as opposed to a sample of it. To the authors' knowledge, this particular method has not been used before to estimate the effectiveness treatment for problem opioid use.

FINDINGS COMMENTARY Internationally the evidence is strong that being in treatment – and especially for opiate users, being in a substitute prescribing programme – helps prevent overdose deaths. Some of the most clear-cut data comes from Scandinavia, where resistance to prescribing opiate-type drugs to heroin addicts has created quasi-randomised, real-world comparisons which permit the value of these approaches to be more convincingly demonstrated than in the UK, where the widespread availability of substitute prescribing treatments makes such a comparison impossible.

The featured study used routinely-collected data to pursue a non-experimental method of estimating the number of lives saved by opioid treatment each year. The counterfactual model enabled the researchers to infer causality at the level of the population, despite not being able to directly observe the event – in this case what would have happened in the absence of treatment. A dip in the proportion of heroin-related deaths was observed in 2010, as well as a rise in methadone-related deaths. This corresponded with a shortage of heroin on the illicit market during this time, affecting heroin-related deaths in England, Wales and Scotland between 2010 and 2013 – an issue explored extensively in this Effectiveness Bank hot topic.

A key assumption the researchers made was that in the absence of treatment, all opioid users would have died at the same rate – including those who did not receive treatment during the year, those who entered treatment and stayed in it, and those who entered but left. This meant that except for age, in every respect other than their treatment access these three groups were considered to be at the same risk of an opioid-related death. If this assumption was incorrect, and what led someone to stay out of or leave treatment would have increased their risk even if they had been in treatment, the consequence would have been to overestimate treatment's potential protective effect.

Another study in England published the same year investigated the relationship between overdose deaths and different treatment states for opioid dependence. The subjects were patients recorded as having received treatment for dependence on opiate-type drugs over four years from April 2005 and March 2009. It found what looked like a *significant protective effect* of treatment, and also conveyed the more specific message that opiate-dependent patients should be engaged and retained in substitute prescribing programmes until there is little risk of their relapsing after leaving. After adjusting for other factors, patients were nearly half as likely

to die (the ratio was 1:1.92) while being prescribed substitute opioids – a finding which led commentators to recognise substitute prescribing as the "gold standard treatment" for opioid addiction, one which informed prospective patients may choose to reject, but which should never be denied them due to lack of access.

Together with the relative numbers in each type of treatment, the results of this study suggest that by far the greatest contributor to the lives saved by treatment are programmes like methadone and buprenorphine maintenance. Not factored into either study was *naloxone* – an emergency antidote to opioid-related overdose, not a treatment for problem opioid use itself. Naloxone rapidly reverses the effects of opiate-type drugs, including the respiratory depression which causes overdose, and can successfully prevent an overdose from becoming fatal. So whilst not a treatment for opioid dependence, it can have an impact on deaths from opioid use. UK law was amended in 2005 to permit emergency administration of naloxone by any member of the public, but much of the practical action taken to extend its life-saving benefits occurred outside the timescale or the context for this study, meaning that naloxone would likely have had minimal impact on the overall picture of opioid-related deaths prevented in England between 2008 and 2011.

Last revised 28 February 2017. First uploaded 09 February 2017

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