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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Effectiveness of Scotland's National Naloxone Programme for reducing opioid-related deaths: a before (2006–10) versus after (2011–13) comparison.

Bird S.M., McAuley A., Perry S. et al.

Addiction: 2016, 111(5), p.883–891.

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In 2011 Scotland became the first country to fund a national policy of distributing the opiate-blocker naloxone to prevent deaths involving opiate-type drugs. According to this evaluation it did prevent deaths where the effect was most likely to be seen – in the weeks after release from prison.

SUMMARY Problem drug users are particularly likely to suffer drug-related death after periods of relative abstinence, most notably soon after being released from prison, but also after discharge from hospital. The most likely reason is loss of tolerance [acquired ability to tolerate large doses after regular use] to opiate-type or 'opioid' drugs, but prison release and hospital discharge may also mark transitions to vulnerability for other reasons.

Key points
From summary and commentary

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A national evaluation found it did prevent deaths where the effect was most likely to be seen – in the weeks after release from prison.

Naloxone is an opioid antagonist which blocks the effects of opiate-type drugs, including effects which lead to fatal overdose. In 2005 it was added to the United Kingdom's list of medicines which though available only on prescription, could nevertheless in an emergency be administered (normally by injecting into muscle tissue) by anyone to save life. The move paved the way for Scotland to implement the world's first centrally funded, coordinated and evaluated national naloxone programme. Implemented from January 2011, across Scotland the programme was standardised on the basis of *British National Formulary* recommendations for intramuscular administration to adults. After completing brief training, individuals at risk of opioid overdose can be prescribed the medication, a practice implemented pre-release in all 15 prisons in Scotland and in services outside prison. Workers in drug services can also supply naloxone kits to protect at-risk patients, enabling supply not just by doctors but more broadly.

Under the national programme, from 2011 Scotland's prisons were resourced to prescribe naloxone on release for 5000 eligible prisoner releases, and 6000 prescriptions a year were envisaged by drug treatment agencies and doctors outside prison. In principle these supplies were sufficient to reach over a third of all Scotland's injectors and totalled at least 20 times more than Scotland's annual number of opioid-related deaths, potentially a very high level of distribution.

The featured study evaluated Scotland's programme by comparing opioid-related death rates in the five years before its implementation (2006–10) with those during its first three years (2011–13). It was decided that variations in the overall opioid-related death rate made it unsuitable as an evaluation metric, and that instead the focus would be on the proportion of these deaths which occurred in the first four weeks after release from prison, and secondarily on the proportion which occurred during that period plus the corresponding period after discharge from hospital. Both are high-risk transitions when the programme can be expected to have made a noticeable difference, especially in relation to releases from prison. Unlike prisons, hospitals were not specifically targeted to prescribe naloxone kits to at-risk clients. As a result, it was thought that dependent opiate users leaving hospital and those around them would have been less aware (so presumably less vigilant) of the heightened risk of fatal overdose than after leaving prison.

If the proportion of opioid-related deaths accounted for by the immediate post-release period fell, this result would be consistent with the programme exerting the desired effect, but would not in itself prove cause and effect. To help determine causality, standard criteria were applied to the results to establish the likelihood that death rate trends were actually caused by the national programme. Additionally, an estimate was made of the cost of the naloxone prescriptions per year of lives saved, adjusted for the quality of those

lives.

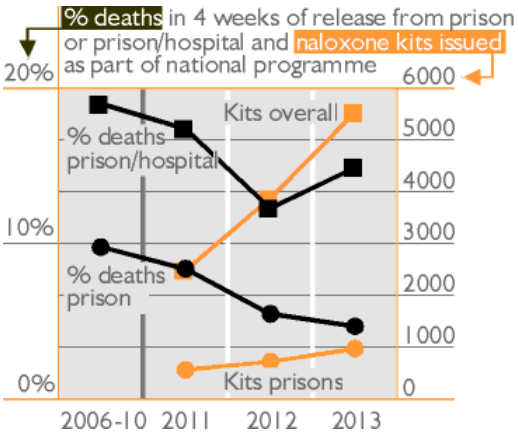
This account also draws on supplementary information published alongside the featured article, the rationale and plan for the study, and a comment on the findings and the authors' reply.

Main findings

To the nearest 100, Scotland issued 2500 naloxone kits in 2011, 3900 in 2012 and 5,500 in 2013. In respect of both the study's chosen indicators (deaths after leaving prison and after leaving prison or hospital), the evidence was that this programme had helped prevent deaths.

Of the 1970 opioid-related deaths before the programme in 2006–10, 193 or 9.8% were of prisoners released in the previous four weeks. Over the first three years of the programme this proportion fell to 6.3% (76 of 1212 deaths), a 36% reduction in the proportion of all opioid-related deaths accounted for by the post-release period ▸ chart. Applying the conventional criterion of a 1 in 20 chance of the real figure being within this range, the reduction might have been from 20% to 51%.

Over the eight years analysed by the study, post-prison deaths formed about half the deaths after leaving either prison or hospital. Before the national naloxone programme, this prison/hospital total formed 19% of all Scotland's opioid-related deaths, a proportion which fell to 14.9% during the programme's first three years – a 22% reduction in the proportion of Scotland's opioid-related deaths accounted for by the period shortly after leaving prison or hospital. Applying the conventional criterion, the real fall might have been from 7% to 33%.



As the number of naloxone kits issued in prison increased, post-prison deaths accounted for a diminishing % of all opioid-related deaths in Scotland.

In respect of post-prison deaths, these figures equate to a mid-point estimate of 42 opioid-related overdose deaths (range 19 to 65) averted by the 12,000 naloxone kits issued during the first three years of the programme, at a current total prescription cost of around £225,000. Assuming that people at risk of overdose experience a quality of life diminished to 70% of the ideal, and that people whose lives were saved by naloxone lived another year, each quality-adjusted year of life saved cost from £4900 to £16,900. If the overdose sufferer lived another ten years, the cost would have been between £560 and £1940.

Of the criteria for establishing the programme actually caused a reduction in opioid-related overdose deaths, the authors of the featured article argued all were at least partially met:
• strength of the link between the reduction in the deaths metric and the national programme;
• consistency, demonstrated by similar results for men and women and different age groups;
• analogy with the effect of similar factors;
• biological gradient, satisfied by the finding that as more naloxone kits came to be issued the reduction in post-prison-deaths also grew;
• a plausible mechanism in the targeting of naloxone at prisoners about to be released who are known to be at high risk of opioid overdose;
• coherence with records from Scotland's needle exchanges, which suggested a 2.5- to 3-fold increase in prescription of take-home naloxone to current injectors between 2011 and 2013, a period over which the featured study found that the reduction in the proportion of opioid overdose deaths occurring after release from prison also tripled; and
• partially, evidence from controlled studies.

The authors focused most on the criteria of 'specificity' and 'temporality'. The former is based on the argument that if a trend or event occurs in relation to the focal intervention but not in other circumstances, then the focal intervention is more likely to have been the cause. In the current case, the measure used to establish specificity was the proportion of opioid overdose deaths within 12 weeks of leaving prison which occurred in the highest risk first four weeks. The naloxone programme was associated with a reduction in this proportion from 73% to 56%. No such reduction was associated with Scotland's prison-based opioid maintenance prescribing policy, supporting the view that the effect was specific to and caused by the naloxone programme.

'Temporality' refers to the need for effect to follow cause and is to that degree satisfied, but there were other potential influences around the same time which could have affected the proportion of opioid overdose deaths accounted for by the period after release from prison. Among these was a law which came into effect from early 2011 which introduced a presumption against custodial sentences of three months or less, a measure which seems in prisons to have affected the drug-related caseload and the extent of opiate use.

The authors' conclusions

In its first three years Scotland's national naloxone programme is likely to have cost-effectively resulted in at least a 20% reduction in the proportion of all opioid-related deaths accounted for by the four weeks after release from prison, and the best estimate is a 36% reduction. As the programme extended to more kits, the post-prison reduction also grew. These results may encourage other nations to adopt naloxone distribution policies.

In contrast, the programme had little apparent effect on deaths after discharge from hospital, perhaps because effects were too small to register, and/or because the risks of this transition are less well known than those associated with leaving prison.

This contrast, and the possibly very low impact on post-prison and post-hospital deaths in total, caution against assuming that the success of the prison component will be replicated in other circumstances.

Cost-effectiveness calculations did not account for the non-prescription costs of the programme including outreach and training, nor of any averted (or additional) costs, such as might be due to fewer attendances at accident and emergency departments. There may also be additional averted deaths not accounted for in the calculations. It is unlikely that any such considerations – apart from possibly increased criminal justice costs – would overturn naloxone's cost-effectiveness as a lifesaver, though extra costs exceeding half the current prescription cost of £19 per kit should be avoided.

In the rest of the UK Wales also has a national naloxone programme but England has not. It has been calculated that to meet the needs of its opiate injectors, England would have to issue at least 9000 naloxone kits a year and ideally 20,000.

FINDINGS COMMENTARY Before knowing the final results of their study, the authors explained how they saw its possible significance: "If Scotland's 3-year results entrench, rather than pull back from, the first two years' reduction in the proportion of [opioid-related deaths] with a 4-week prison antecedent [the] evaluation could shift the policy ground so seismically that it would call into question the continued absence of funded [take-home naloxone] schemes in other countries." In the event the downward trend continued, in their eyes calling in to question why other countries – presumably including England – have failed on national scale to take this action to save the lives of opiate users. During and after the study period, trends in deaths after release from hospital gave no indication that the programme had helped. Total opioid-related deaths also increased in 2014, calling into question whether the evidence shows that overall the programme has had the desired effects, even if the small minority of deaths which occur after release from prison have been reduced.

However, given what we know of naloxone's effects and its record (1 2) in programmes similar to that in Scotland, it seems implausible that the distribution of around 12,000 kits over three years would have failed to help prevent opioid-related deaths, and likely that the well-publicised and well defined risk period after prison would have been a time when the programme had a chance to make a difference, and when ex-prisoners and their associates would have been most alert to the risks and most ready to counter them. This plausibility alone could be considered enough to justify national programmes with a linked evaluation, even in the absence of proof in advance that the programme will save lives.

Does the data support the conclusions?

Being able to explain why post-prison deaths were proportionately reduced, but not those after leaving hospital, is important if the former is to be accepted as evidence of the programme's success, without also having to accept the latter as evidence of its failure.

Opioid-related deaths in the four weeks after prison release were chosen as the basis for the primary yardstick of the naloxone programme's success because prison release is well established as a high-risk period during which effects might be noticeable. The proportion these formed of all opioid-related deaths was chosen as the specific metric, because while the *number* of deaths may fluctuate for many reasons, including the 'heroin drought' which occurred during the study period, the *proportion* of these accounted for by the post-prison period will not be similarly affected, so will more directly reflect the impact of the naloxone programme. Further reasons for expecting effects to be concentrated in post-prison rather than post-hospital periods were that the post-prison risk was about twice as high, that prisons had been systematically targeted by the naloxone programme in a way other institutions – and specifically hospitals – had not, that hospitals had no protocols for routinely issuing naloxone kits to at-risk patients, and related to this, that people with a history of injecting would be less aware of the heightened risk of fatal overdose after leaving hospital than after leaving prison.

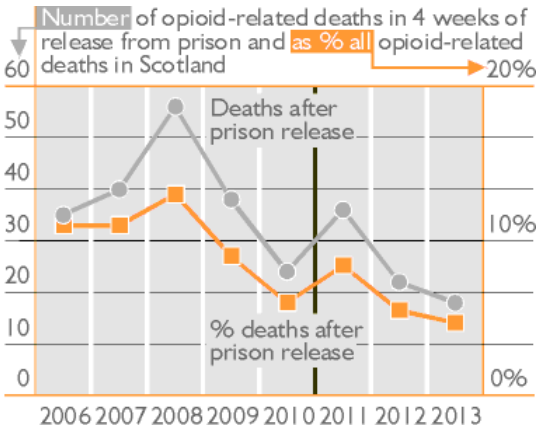
Only if systematic targeting of prisons to issue kits actually worked would it help explain why

the programme was more effective in the post-prison period than at other high risk periods not specifically targeted. Prisons did indeed seem to have major advantages as implementation sites. They had a captive audience who could be recruited into the necessary training to use the kits, and on completion a kit could be placed with each prisoner's belongings, taken with them on release. But in practice, even the best-performing prisons distributed only half the number of kits expected from their notional number of released opiate-dependent inmates. Based on a target set in 2014/15, the potential total is around 6800 a year if each opiate-dependent prisoner is issued a kit on release, but in the study period the number distributed each year ranged from 570 to 978. Outside prison the total ranged from 1917 to 4555, short of the planned 6000 a year which was enough for about a third of Scotland's injectors. Given these figures, it is questionable whether the programme was better implemented inside than outside prison.

Further evidence that prisons implemented the programme no better than non-prison settings comes from surveys of needle exchange attendees in Scotland. These showed prisons were an important source of kits, in 2013–2014 supplying nearly 1 in 5 attendees with their most recent kit. Once the short average five-month sentence had been taken into account, in both 2011–2012 and 2013–2014 the chances that an injector had received a naloxone kit on release from prison were very similar to the chances of receiving one during 12 months outside prison. Both rates increased substantially between the two periods. For the analysts it mean that "community services and prisons were equally efficient at targeting their naloxone supplies" to injectors.

However, implementation rates in prisons may not have affected post-prison deaths as much would be expected, because the survival of released prisoners could have depended mainly on the success of the wider programme. In both England and Scotland, twice as many of the kits issued to prisoners are used by them to save someone else rather than used on the prisoner, and the ratio is considerably higher for kits issued outside prison. The implication is that it is the general availability of naloxone kits among drug injecting circles that matters, more than whether the individual at risk has been issued one.

Interviews with staff and service users involved in the national naloxone programme revealed that prisoners often refused participation because of competing activities or because they saw themselves as having moved on from drug using circles. The report commented that "the number of kits distributed in prisons ... appears low" and there was a need to find ways to increase take-up of naloxone training and supply for those leaving prison.



Opioid overdose deaths after leaving prison and the proportion these form of all such deaths were falling before the naloxone programme began in 2011.

A weakness acknowledged by the researchers is pinning down the reduction in the proportion of all opioid-related deaths occurring after prison to the advent of the naloxone programme. It seems equally valid to see the figures as reflecting pre-existing downward trends in both the number of post-prison opioid-related deaths and the proportion these form of the total – trends which began in 2009, well before the naloxone programme, and which continued with a blip upwards in the programme's first year ▸ chart. In this scenario, something other than the programme initiated the downward trends and continued to exert its impact, regardless of the existence of the programme.

Post-prison deaths reduced but no evidence on overall deaths

The study was unable to show that post-hospital deaths had been reduced by the programme, despite this being a high-risk period. The positive findings were confined to post-prison deaths, which formed just 1 in 10 of all opioid-related deaths before the naloxone programme began, leaving it unclear whether it had helped counter the circumstances which led to 9 in 10 of the deaths potentially preventable by naloxone administration. However, according to the researchers' own calculations, the programme they had evaluated was underpowered. For naloxone to be available at every witnessed opiate overdose, ideally Scotland would have supplied 8,000 kits every year and at a minimum 3,600. In the first year of the programme the amount fell well below even the minimum and in none of the three years did it approach the ideal. Matching this ideal

would have meant distributing 24,000 kits across the three years, but in fact the number was about half this.

Another disappointment is that the year after the study period ended, in 2014 the number of opioid-related deaths as defined by the study increased from the previous year by 17% to 449, the highest ever recorded and 14% up on the average for the five years before the naloxone programme.

Also in 2014, the main indicator used by the featured study – the proportion of all opioid-related deaths accounted for the four weeks after prison release – fell once again to just over 3%, signalling according to the featured article's logic the continuing success of the naloxone programme. However, once again the trend in deaths after release from hospital gave no such indication. Together with the overall increase in deaths, these findings call into question whether overall the programme has reduced opioid overdose deaths.

Reluctance to carry kits may have undermined impact

Another study of Scotland's national naloxone programme used surveys of needle exchange attendees in 2011–12 and 2013–14 to assess the reach of the programme and whether having been reached and prescribed a naloxone kit, attendees then put themselves in a position to use it by carrying it around with them. Findings suggest reluctance to carry the kits may have undermined the programme's potential to save lives, though not as much as might be thought due to the preponderance of deaths in the home.

One encouraging finding in the survey results was that the proportion of needle exchange attendees who said they had been prescribed a kit within the past year increased significantly from 8% in 2011–2012 to 32% in 2013–2014. But though there were more kits in circulation, between those time periods far fewer were carried around by the recipients.

The proportion of attendees who were carrying naloxone with them on the day they were interviewed decreased significantly from 16% in 2011–2012 to just 5% in 2013–2014. This pattern was evident across all sub-groups with the exception of those who had been recently homeless. As might be expected, the great majority of attendees were current or recent injectors. Among the minority who had injected in the past but not in the last six months very few carried the kits they had been prescribed – in 2011–2012 just 5%, and in 2013–2014, just 1%, the latter figure representing one person out of 81. But even among more recent injectors, in 2013–2014 just 6% were carrying a kit when interviewed.

The naloxone kit used in Scotland is bulky and bright yellow – hardly unobtrusive and not easily portable

What caused the drop in the carriage rate between 2011–2012 and 2013–2014 the analysts could only speculate. Reluctance to be associated with injecting among recovering or recovered drug users seems an unlikely explanation, since all the sample were interviewed at needle exchanges, and though it could account for the overall low carriage rate, it is hard to see how it could account for the fall. Reluctance to be spotted as an injector by being seen or apprehended with the bright, bulky kits (▸ illustration) could also have contributed to the low overall rate. Allied with the presumption that with so many kits around in 2013–2014, someone else will have one handy, it may also have contributed to the reduction in the carriage rate as more injectors felt justified in leaving the responsibility and risk to someone else. Possibly too, prior experience of having carried a kit around but never found a use for it might have led to the fall.

A trial in Britain of prison-release naloxone packages the pre-filled syringe and related information in a special wallet which also functions as a regular wallet, less obtrusive packaging which users may be more likely to take with them because they also use it as a wallet. Of 112 prisoners who completed follow-up surveys when reimprisoned within six months, 71% said that in the first two weeks after release they had carried the naloxone kit around with them, seemingly corresponding to the 69% who had returned to heroin use during that period. Another 654 had not returned survey forms. How many of the missing prisoners carried the drug around with them is unknown, as is whether carriage was maintained beyond the first two weeks, but the results that are known suggest high carriage rates can be engineered.

Though universal carriage may be the ideal, in England in 2013 around 70% of

drug-related deaths occurred in the person's home or at another private residential address, such as a friend's home. In Scotland in 2014, two-thirds of the people who died a drug-related death had taken their drugs (67%) and died (63%) in their own homes. In these circumstances, a naloxone kit may be present even if not carried about in pockets or handbags.

Future uncertain

In Scotland central government support for the scheme has now ended, and it is expected that local health authorities will fund it as a routine measure, a transition feared to lead to more limited coverage. Experience is that general practitioners have been slow to prescribe it for their patients, disappointing as this route is one way of circumventing budget restrictions and cutbacks.

The Scottish Drugs Forum's naloxone web site offers more information on naloxone programmes generally and in the Scottish context. An Effectiveness Bank hot topic has reviewed issues relating to overdose prevention, and another has focused on naloxone programmes.

Thanks for their comments on this entry in draft to Roy Robertson, general practitioner specialising in addiction treatment in Edinburgh, Scotland, and to research author Andrew McAuley of NHS Health Scotland for the information which prompted a revised text. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

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