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. The summary conveys the findings and views expressed in the study. Below is a commentary from Drug and Alcohol Findings.





## ▶ Criminal justice outcomes over 5 years after randomization to buprenorphine-naloxone or methadone treatment for opioid use disorder.

**Evans E.A., Zhu Y., Yoo C. et al.**

**Addiction: 2019, 114, p. 1396–1404.**



*Can a limited period of being prescribed opiate-type medications generate longer term reductions in the criminal behaviour of patients dependent on illegal opiates like heroin? And of the two main medications – buprenorphine and methadone – which performs best? It seems a key factor is how well they retain patients in treatment.*

**SUMMARY** Opioid substitution therapy involves prescribing medications with similar effects to the opiate-type drugs on which the patient has become dependent, but are legally sourced and less damaging and disruptive to their life. When opioid substitution therapy meets its goal of stabilising patients, illicit opioid use generally decreases, as does the need to commit crimes to support illicit opioid use, such as theft, forgery, fraud, handling stolen goods, and prostitution (1 2). However, as not all opioid substitution therapies work in the same way, the type of medication might make a difference to outcomes, for example via differences in how well they retain patients in treatment.

Buprenorphine–naloxone has a different effect and safety profile than the more widely known opioid substitute, methadone. While methadone is a 'full opiate agonist', producing greater opiate-type effects the higher the dose, buprenorphine is only a 'partial opiate agonist', creating a ceiling of opiate-type effects, attenuating the effect of on top heroin use, and limiting the respiratory depression typically responsible for overdose deaths. Typically these medications are prescribed for an indefinite period on a 'maintenance' basis. However, the featured study examined time-limited treatment, comparing people randomly allocated to maintenance doses of methadone versus buprenorphine for less than six months. In this sub-study the aim was to assess the treatments' relative impacts on crime five years from allocation to treatment.

**Key points**
**From summary and commentary**

The featured study examined criminal justice outcomes five years after participants had been randomly allocated to either methadone or buprenorphine as treatment for opioid dependence.

Continued treatment was associated with a reduction in arrests relative to no treatment.

Findings suggest that treatment of opioid use disorder with either medication is superior to no pharmacotherapy.

The parent study, known as the Starting Treatment with Agonist Replacement Therapy (START) trial, had focused on the medications' effects on the liver health of patients, addressing concerns about a link between buprenorphine and drug-induced hepatitis. Across nine treatment programmes located in five states in the United States (California, Oregon, Washington, Pennsylvania and Connecticut) between 2006 and 2009, 1,269 patients were allocated to receive either buprenorphine (740) or methadone (529). They received the medications for 24 weeks and were then tapered off over up to eight weeks or referred for ongoing treatment. While initially the distribution was one buprenorphine participant to every one methadone participant, it was changed midway to a ratio of two buprenorphine participants to every one methadone participant due to a higher rate of dropout in the buprenorphine arm of the trial.

Other long-term outcomes of START participants had been examined in another sub-study where the focus was mortality and illicit opioid use. An average of five years after starting opioid substitution therapy, the researchers found no significant difference between patients allocated to buprenorphine versus methadone in their rates of mortality or illicit opioid use. However, treatment retention was not as good among those assigned to buprenorphine (1 2), a finding consistent with other research (1 2 3 4).

The featured study followed-up a small cohort of participants from the START trial – 179 randomly allocated to buprenorphine and 124 to methadone at three clinics in California, the only state which could supply administrative data on criminal justice outcomes. Participants were followed up between two and eight years after first being randomised, averaging 4.5 years. Unless indicated otherwise, the findings reported below are based on an analysis of all participants who were followed-up (74% of those contacted) regardless of whether they had received their allocated treatment.

## Main findings

Though similar in other ways, at the start of the trial there was a significant difference in the proportion of participants testing positive for cocaine in the buprenorphine and methadone groups (29% vs. 40%). One-third of participants were female, the average age was 42, more than half were white, 95% tested positive for opiates, approximately 80% had injected drugs in the prior 30 days, approximately 66% had been arrested, and 39% had been imprisoned.

As in the parent study, during the five-year follow-up period patients randomised to buprenorphine spent significantly less time in medication-based treatments for opioid use than those randomised to methadone: they were in treatment during 49% of months versus 57%, and averaged 29 months in total compared to 34.

Despite this, over the five-year follow-up there had been little difference between those allocated to buprenorphine and methadone in the proportions arrested (55% and 54%) or imprisoned (41% and 47%). On average participants in both groups had been arrested twice – most often for drug-related crimes – and had been imprisoned for an

average of five months. The likelihood of arrest decreased with each additional month of time that went by in the follow-up.

In the 30 days prior to follow-up, there was no difference between the groups of participants in their reported criminal justice involvement. Few participants in both groups reported an arrest (approximately 2%) or criminal involvement (6–7%), and 14–18% were on probation or parole.

Another set of analyses focused on patients who had actually received methadone- or buprenorphine-based treatment, as opposed to those allocated to these treatments but who may not have received them during all or part of the trial period and/or who switched medications. These analyses do not benefit from the 'level playing field' intended to be created by randomised allocation, so any findings would need to be tested in a study designed to be able to adequately assess their validity.

People who received buprenorphine or methadone treatment were significantly less likely to be arrested than people who did not receive treatment:
• Unlike the 'no-difference' finding based on allocations to the treatments, in months when they were actually receiving buprenorphine, patients were significantly and substantially less likely to be imprisoned than those who received methadone.
• Among people allocated to methadone, arrest was significantly less likely with receipt of methadone during follow-up (relative to no treatment during follow-up). This was also true for people in the methadone group who switched to buprenorphine.
• Among people allocated to buprenorphine, arrest was significantly less likely with receipt of buprenorphine during follow-up (relative to no treatment during follow-up). People who switched to methadone had a similar likelihood of arrest as receiving no treatment.

## The authors' conclusions

Being in treatment with opioid substitution therapy – whether methadone or buprenorphine – was associated with better criminal justice outcomes five years later than not being in treatment. Furthermore, continued treatment was associated with a reduction in arrests relative to no treatment.

**FINDINGS COMMENTARY** Methadone and buprenorphine are evidence-based medications – designated by the World Health Organization as essential medicines in the management of opioid dependence. Uncertainty about their relative benefits, allied with differences in the safety and effects of the drugs, suggest that some patients will be best suited to methadone, others to buprenorphine. Unfortunately, there is little in the research to indicate who will be in which camp. While the featured study found that people who received buprenorphine during follow-up were less likely to be imprisoned than those who received methadone, overall, its findings seemed to support the theory that being in opioid substitution therapy – whether methadone or buprenorphine – is better than not being in opioid substitution therapy at reducing an opioid-dependent person's involvement in crime and the criminal justice system over the longer term. As the authors put it:

> *"In a US sample of people treated for opioid use disorder, continued treatment with either buprenorphine or methadone was associated with a reduction in arrests relative to no treatment."*
>
> *"This study shows that continued treatment for opioid use disorder with either buprenorphine or methadone is associated with a reduction in arrests (relative to no treatment)."*

The featured study followed-up a small cohort of participants from the START trial, which was originally designed to examine the liver health outcomes of methadone and buprenorphine among opioid-dependent patients. START was a 'phase four' clinical trial, which is one of the later stages in a clinical trial where research had already demonstrated that a treatment works and the treatment has been licensed (in this case by the US Food and Drug Administration). Phase four clinical trials aim to find out more about safety and side effects, the long-term risks and benefits, and how well treatments work when used more widely. This trial did not need to include – and indeed did not include – a control group, which has implications for the way the findings are interpreted. Without a control group there was no benchmark of how participants would have fared if randomly allocated to 'no treatment'. Instead, the researchers compared participants who had received treatment during the 60-month follow-up period with participants who received no treatment despite being originally allocated to receive at least 24 weeks of treatment. This is important if we return to one of the main conclusions, which was about the benefits of being in opioid substitution therapy versus not being in opioid substitution therapy. The study was evidently not designed to investigate this or come to a conclusion about it:
• The clinical trials records did not include an aim to evaluate opioid substitution treatment against no treatment (1 2).
• The design of the study means we cannot rule out that factors outside of the binary question of 'treatment or no treatment?' impacted participants' recovery and criminal justice outcomes. For example, people who participated in treatment may have had different levels of motivation, readiness to change, self-efficacy, and access to resources than those who did not or could not participate in treatment.

### Random allocation of opioid substitutes: removes potential source of bias, but does not reflect real life

During the course of the follow-up, participants were randomly assigned to receive either buprenorphine or methadone. Random allocation ensures that participants have an equal chance of being in one group or another. This design helps to limit the effect that differences in participants will have on the outcomes. However, in this case random allocation represented a major departure from prescribing under real-life circumstances. For this reason, the findings may not have reflected the potential of buprenorphine or methadone if they had been chosen by patients and clinicians.

The design of the START trial had to be amended partway through due to the relatively high rate of dropout in the buprenorphine arm – perhaps indicating a difference in preference for methadone and buprenorphine. Overall, participants spent a smaller proportion of time in buprenorphine treatment than methadone treatment (12% of months vs. 38%). Furthermore, despite being allocated to buprenorphine these patients spent a greater proportion of their time in methadone than buprenorphine treatment (16% vs. 30%), whereas people in the methadone group spent a greater proportion of time in methadone treatment than buprenorphine treatment (48% vs. 7%).

Buprenorphine works in a different way to methadone, setting a 'ceiling' on opiate-type effects. This will not appeal to everyone who is dependent on opioids. People wanting to divorce themselves from opioids in general (ie, to do without opiate-type effects) are more likely to choose buprenorphine, which may also help to account for the finding that people who received buprenorphine during follow-up were less likely to be imprisoned than those who received methadone.

During the course of the follow-up, participants were able to receive pharmacotherapy additional to that facilitated by the START trial – sometimes switching from buprenorphine to methadone, or from methadone to buprenorphine. This 'treatment switching' arguably introduced a barrier to being able to compare a 'pure' sample of methadone participants with buprenorphine participants.

### Does treatment reduce crime by reducing drug use?

Despite the featured report's claims of positive criminal justice findings, over half of buprenorphine and methadone patients (55% and 54% respectively) had been arrested by the five-year follow-up, and nearly half had been imprisoned (41% and 47%) – figures indicating that a substantial portion of participants had continued to be involved in or given cause to be suspected of criminal activity. While this could be perceived to put a damper on claims of the protective effect of opioid substitution therapy, one could argue there is an important qualification: the greatest proportion of arrests were drug-related, so may have reflected incomplete remission from the opioid use problem which led the patients into treatment rather than unabated resort to crime to fund illegal opioid use or an unresolved criminal lifestyle. To frame it in a slightly different way, it could also be argued that arrests cannot necessarily be seen as a reflection of the criminal inclinations of people with substance use problems, but rather highlight one of the implications of criminalising people with substance use problems.

In the UK, answers to whether crime can be reduced by reducing drug use have predominantly come from the Drug Treatment Outcomes Research Study (DTORS). Set in England in 2006, DTORS assessed the progress of patients starting drug treatment in England. Rather than setting up treatments to be tested on patients allocated by researchers, the study simply tracked what happened after patients presented in the normal way to usual drug treatment services. DTORS found crime went down as the need to commit it to raise money for drugs also fell, but strangely there was no clear correlation between the criminal income of each participant at different stages in the study and the extent of their drug use.

This causal chain between drug use and crime seemed supported by the way that, over the follow-up period, drug use, spending on drugs, crime, and income from crime all fell, and generally the more so the more time a patient had spent in treatment. The obvious explanation was that crime was driven by the 'need' to offend to support drug use, and that once drug use was curbed, the need for crime and crime itself waned. The figures were consistent with this explanation. Before treatment, patients typically spent £188 more per month on drugs than they legally earned, a shortfall expected to be filled by income from crime. But within three to five months, the same people were typically earning £140 more per month than their current drug spend, so had less need to resort to crime. The same processes should have resulted in a clear correlation between the criminal income of each participant at different stages in the study and the extent of their drug use. However, this was not the case:

> *"Treatment appears to be associated with significant reductions in income from offending. However, no direct correlation with levels of drug use was distinguishable within these data".*

Depending on the exact measures found not to be correlated, part of the explanation may be that offending and drug use (though still substantial) had already been reduced before the study, either on the initiative of the treatment-seeker or because they were restricted by criminal justice supervision.

### Maximal protection may hinge on duration

The featured study investigated the outcomes of patients offered time limited treatment, which is arguably an example of how *not* to do methadone and buprenorphine prescribing. International research evidence indicates that: longer treatment periods are associated with improved outcomes (including reduced use of other opioids and reduced criminal activity); and time-limiting opioid substitution therapy could have serious negative unintended consequences with very little evidence that it would be beneficial.

While from the UK there is evidence that buprenorphine-based treatment may be associated with lower rates of overall mortality than methadone-based treatment, including the first four weeks when patients are presumed to be at greatest risk, across the population buprenorphine is unlikely to give greater overall protection because of the relatively short duration of treatment (an average of 173 days vs. 363 days). In UK primary care, most patients receive relatively short durations of opioid substitution treatment, and this is particularly the case among patients prescribed buprenorphine. It is this combination of short average treatment durations and high mortality risk in the period after treatment cessation that led the researchers on this UK study to conclude that neither buprenorphine nor methadone (in their current offerings) can further impact the number of drug-related poisoning deaths in the UK population. However, this is not to be mistaken with the conclusion that opioid substitution makes no difference; far from it.

The above study about relative rates of mortality in buprenorphine- versus methadone-based treatment did not involve or make comparisons with dependent opioid users who rejected treatment altogether – 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 the mortality rate among the never-treated as well as before treatment for those treated, and found treatment strongly associated with lower mortality. 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.

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