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.

▶ Weekly and monthly subcutaneous buprenorphine depot formulations vs daily sublingual buprenorphine with naloxone for treatment of opioid use disorder: a randomized clinical trial.

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In the new form of extended-release injections whose effects last up to a month, the opioid medication buprenorphine was found to suppress illegal opioid use more effectively than the standard daily regimen.

SUMMARY Opioid use disorder can be treated effectively with sublingual (taken by dissolving under the tongue) buprenorphine, a medication which can substitute for heroin and other opioids. Despite its efficacy, currently approved forms of buprenorphine intended to be taken daily have limitations, including daily peaks and troughs in the drug's presence in the body, patients not taking medication as prescribed, medication being passed on ('diverted') to other people or injected, and unintended consumption by children. These limitations may reduce effectiveness, and contribute to negative perceptions of the treatment, stigma affecting patients, and barriers to treatment uptake.

Key points
From summary and commentary

The opioid medication buprenorphine suppresses illegal opioid use and retains opioid-dependent patients in treatment.

However, daily buprenorphine regimens risk patients not taking the medication or it being passed on ('diverted') to other people, and may require daily attendance at a clinic or pharmacy.

Extended release injectable buprenorphine largely avoids these risks. In this randomised trial, it was more effective at suppressing illegal opioid use than the standard daily sublingual (under the tongue) delivery regimen.

Other ways of taking buprenorphine are being tested which might wholly or partly overcome these limitations – in particular, extended-release forms injected under the skin whose effects last a week or a month. Based on a product known as CAM2038, these cause few problems at the injection site or while circulating in the body and deliver a steady dose proportional to the amount injected. For example, a single 24 mg weekly injection or 96 mg monthly injection of CAM2038 delivers a similar dose exposure as 16 mg a day of sublingual buprenorphine.

Over 24 weeks, the featured trial set out to test whether these new extended-release forms really do work better than conventional sublingual products. Adult patients enrolled in the trial at 35 outpatient clinical centres in the USA in 2015 and 2016. They had to be seeking treatment for moderate to severe opioid dependence and have medical and psychosocial histories considered to make them good candidates for buprenorphine-based treatment. Among other exclusion criteria were recent or current suicidal ideation or behaviour, and pending legal action or anything else which could adversely affect safety or prevent adequate adherence to the treatment. The trial's 428 participants were typically men in and around their late 30s. Only about a third were employed, two-thirds had

been arrested, and half had injected opioids. Seven in ten were primarily using heroin, but other drug use was common.

A randomly selected half of the patients were allocated to sublingual placebos but real buprenorphine injections, while for the other half the injections were placebos and the sublingual doses were real buprenorphine combined with naloxone [known in the UK as Suboxone] to make it less likely to be injected. The aim was to ensure that patients and their evaluators would not know what they were taking, eliminating their expectations or disappointment as factors in the outcomes, throwing into profile the effects of the medications themselves.

In the first week of the treatment the aim was to work up to doses equivalent to 16 mg a day of buprenorphine. Then (as in normal clinical practice) doses were flexible, based on patient needs and clinical judgment. During weeks one to 11 patients were scheduled to visit the clinics weekly for their injections and to be given a week's supply of the sublingual product. During the remainder of the trial visits were monthly; patients switched to the monthly forms of the injections, were given a four-week supply of the sublingual products, and both sets of patients could if needed be administered supplemental 8 mg injections of extended-release buprenorphine. Unlike the randomised doses, patients knew these were the active medication.

During the weekly phase patients were allowed to be two days late for appointments and in the monthly phase a week before a decision was made about whether they could safely continue treatment. After 24 weeks standard clinical care was offered until patients were followed up at 28 weeks after the start of treatment. All participants received manual-guided, individual addiction counselling at each visit, and were asked to submit urine for testing. Additional random tests were conducted during the monthly phase of the treatment. Attendance allowances averaging $50 per visit per patient were paid.

The primary yardsticks of the success of the treatments were the average proportion of urine samples negative for illicit opioids during the 24-week medication period, and whether the patient was responding well to treatment. 'Responders' had to have no evidence of illicit opioid use from urine tests or their own accounts for at least two out of the three assessments during weeks nine to 11 and at week 12, and for at least five of the six assessments from weeks 12 to 24, including the final four weeks of treatment. For the primary analyses missed urine tests (just over a quarter were missed) were counted as indicative of illicit opioid use, but the data was also re-analysed by simply missing these tests out. Based on these yardsticks and also on retention the researchers assessed whether there was reliable evidence that extended-release buprenorphine was inferior to the standard sublingual form.

Main findings

All 428 patients got to the point of at least starting their medication and around 70% (about the same whichever medication they had been allocated to) completed the 24 weeks of the study. At the equivalent of 18–20 mg a day of buprenorphine, average doses were about the same for both sets of patients, and on average both attended about 95% of their counselling sessions.

There was no evidence that extended-release buprenorphine was inferior to the sublingual form. To the contrary, based on urine tests in weeks four to 24 of the trial, the extended-release form was significantly better (35% tests negative versus 27%) at suppressing illicit opioid use. Combining urine test results with the patients' own accounts confirmed this advantage, as did an analysis confined to patients injecting at entry to the trial. However, the extended-release form was only slightly and non-significantly better on the yardstick of responding well to treatment (37% versus 31%), and there were no significant differences in how intensely patients wanted to take opioids, desires which substantially attenuated throughout the trial. Whichever form of buprenorphine patients had been allocated to, withdrawal symptoms were suppressed immediately.

Among the generally non-severe adverse events were five non-fatal drug overdoses, all among patients allocated to sublingual buprenorphine. Adverse events led 10 of the 428 participants to discontinue the study's treatments; eight were due to problems at injection sites or occurred among patients allocated to extended-release buprenorphine.

The authors' conclusions

Extended-release injectable buprenorphine was not shown to be less effective than the standard daily sublingual delivery regimen at suppressing illegal opioid use and retaining patients in treatment. Relieving patients of the daily choice whether to take the medication had the intended effect of augmenting its efficacy. Extended-release buprenorphine also generated similarly rapid suppression of opioid withdrawal and craving in the first week and throughout the trial. Few patients received supplemental injections, suggesting that doctors could individualise and titrate weekly and monthly injection doses as they did daily doses of sublingual buprenorphine-naloxone. In normal practice, treatment retention and outcomes might improve further because patients would know what they were taking and not have to take daily placebo tablets.

The safety profile of extended-release buprenorphine was generally comparable to that of sublingual buprenorphine-naloxone, with the exception of some mild-to-moderate injection-site reactions, most commonly transient pain. Of note were the five non-fatal overdoses, all among sublingual patients. One occurred in the context of withdrawal after being jailed and not having access to study medication[, less likely to happen with the extended-release form].

Good candidates for extended-release buprenorphine include people at risk of unwanted disruptions in treatment and/or loss of opioid tolerance (eg, during imprisonment or residential treatment), who have difficulty adhering to or dislike taking daily medication, who are unable to safely store their medication, concerned about theft of the medication or disclosure of their treatment (eg, while travelling or at the pharmacy), or who may divert, abuse, or inject their medication. Extended-release buprenorphine may also reduce some of the burden and stigma imposed on patients by having to take medication daily, which in some treatment settings involves attending the clinic for administration to be supervised.

FINDINGS COMMENTARY As expected, extended-release injections which ensure medication adherence for a week or a month were better at suppressing ‘on top’ opioid use than a regimen affording daily opportunities to miss the medication. What was surprising was that this advantage was so small. The ‘responder’ rate was the primary yardstick specified in the trial plan, and on this basis there was no statistically significant or substantial advantage for the injections. The statistically significant difference in the proportion of urine tests positive for opioids was also minor; just 7% more of the tests scheduled for patients allocated to injections were negative.

One reason for the modest gains might be that patients had been handpicked to be good candidates for buprenorphine-based treatment and to be able to follow the intended treatment, which overwhelmingly they seem to have done, perhaps encouraged by expenses to attend study visits into more consistent attendance than might normally be expected. Participants received addiction counselling at scheduled weekly and monthly study visits and around 95% of people in each group attended scheduled sessions. Many were perhaps going to do well in any event on sublingual buprenorphine-naloxone, and did not need the extra security against relapse provided by the extended-release formulations. In the monthly phase of the trial, the few who did need this could get it even if allocated to sublingual medication delivery. Attendance would have been aided by attendance allowances which would have cumulated to (for an unemployed person) a substantial sum.

Nevertheless, clearly there was considerable room for improvement in outcomes: most patients took illegal opioids and most did not respond well to treatment according to the study’s criterion. Extended-release buprenorphine made minor inroads into this potential. One notable advantage for extended-release buprenorphine not stressed by the researchers was the significant difference in injecting. Over weeks four to 24 of the trial, twice (31% v. 15%) as many of the assessments of extended-release patients indicated no injecting – a substantial potential benefit in injecting-related ill-health, including spread of disease.

As the researchers pointed out, instead of among relatively compliant patients in the trial, extended-release injections would seem to have their greatest potential among less stable patients – those unlikely to take daily doses and perhaps even less likely to regularly attend a pharmacy for consumption to be supervised. In the

trial, one of the great advantages of the injections for the patient – not having to attend several times a week for supervised consumption – was negated because neither set of patients were required to do this. If frequent supervised consumption is the alternative, patients who would otherwise not enter or stick with treatment might be prepared to give the injections a try, possibly benefiting from reduced use of illegally obtained opioids.

Under the trade name Buvidal, on 20 November 2018 extended-release buprenorphine injections were authorised to be marketed in the European Union for the treatment of opioid dependence, a decision made mainly on the basis of the featured trial. In turn Buvidal was licensed to be marketed in the UK, and in February 2019 NICE, the UK's health product assessor, had issued guidance, again based on the featured study. NICE's experts noted that the recommended ceiling dose of Buvidal may not be enough for some patients, and that the cost of providing this medication greatly exceeded sublingual buprenorphine and oral methadone, though there would be savings due the reduced need for supervised consumption. Some of the experts considered the preparation most likely to be suitable for patients who might sell or pass on other opioid medications, where there were concerns about these being stored at home, difficulties adhering to daily supervised administration, or for patients who are stable on a therapeutic dose of sublingual buprenorphine or live in areas without easy access to a pharmacy.

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