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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▶ Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial.

Fiellin D.A., Schottenfeld R.S., Cutter C.J. et al.

JAMA Internal Medicine: 2014, 174(12), p. 1947–1954.

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Among patients dependent on prescription opioids, ongoing maintenance therapy using a legal opiate substitute (buprenorphine–naloxone) produced better outcomes than tapered withdrawal, with patients less likely to have used illicit opioids and considerably more likely to have remained in their allocated treatment.

SUMMARY Drug overdose is a leading cause of accidental death in the United States, with most of these deaths due to prescription opioids (1 2). However, limited research data is available to guide the decisions that physicians and patients routinely make between facilitating medication-assisted withdrawal from opioids (also known as 'tapering') and ongoing maintenance treatment.

Studies with patients dependent on heroin have demonstrated improved outcomes with methadone maintenance therapy compared with methadone taper (3 4), including reduced mortality, risk of HIV transmission, and criminal behaviour (5 6 7). Patients dependent on prescription opioids can differ in important ways, however, often having shorter histories of opioid dependence, lower levels of physical dependence, better occupational and social functioning, and improved treatment outcomes (8 9 10 11) – leading to questions about whether they might require ongoing maintenance treatment or might instead benefit more from shorter-term taper followed by continued counselling and treatment with the 'opioid-blocking' drug naltrexone.

To aid the development of evidence-based guidelines for patients dependent on prescription opioids, the featured study compared medication-assisted withdrawal using buprenorphine with buprenorphine maintenance treatment in a primary care setting, assessing the subsequent illicit use of prescription opioids.

Key points
From summary and commentary

This study compared the effectiveness of two applications of buprenorphine–naloxone – medication-assisted withdrawal (also known as 'tapering') and ongoing maintenance treatment – for treating the illicit use of prescription opioids.

Patients responded best to ongoing maintenance therapy. They were considerably more likely to remain in the trial, and less likely to have used illicit opioids during treatment.

Researchers concluded that policies which restrict access to, or place arbitrary limits on, the duration of maintenance treatment should be reconsidered given the relatively poor outcomes of buprenorphine-assisted withdrawal.

A tablet formulation of buprenorphine–naloxone was used in a 4:1 ratio of buprenorphine hydrochloride to naloxone hydrochloride. [If taken as intended, the naloxone component remains inactive, and is there to deter misuse, any injecting, or diversion of the medication to other people.]

For all patients, treatment started with a two-week induction and stabilisation period, at a target dose of 16 mg of buprenorphine hydrochloride per day (though the average in practice was

15 mg per day). During this time, patients underwent evaluation and education by nurses in brief (5–10 minute) sessions, three times a week.

After the induction and stabilisation period, patients were assigned at random to receive gradual withdrawal or maintenance therapy.

Patients assigned to the taper group:
• were offered a stable dose of buprenorphine–naloxone for an additional four weeks followed by a gradual taper (2 mg decrease every three days) for three weeks;
• were provided prescriptions to use for opioid withdrawal symptoms (including anti-sickness medication and a sleeping aid).

Those who achieved seven days or more of opioid abstinence after their last dose of buprenorphine were also offered oral naltrexone (25 mg on day one, followed by 50 mg per day). The availability of injectable naltrexone was discussed with these patients.

Patients assigned to the maintenance condition:
• were offered a further 14 weeks maintenance prescribing of buprenorphine–naloxone at doses which could be raised to 20 or 24 mg per day depending on patient comfort or evidence of ongoing (for three successive weeks) illicit opioid use.

All patients received physician and nurse support and drug counselling.

Main findings

On average patients allocated to the tapering programme left treatment sooner than those allocated to maintenance (staying 58 vs. 99 days after randomisation).

Overall, patients assigned to receive a buprenorphine–naloxone taper were less likely to submit urine samples indicative of abstinence from illicit opioids than patients assigned to buprenorphine–naloxone maintenance (35% vs. 53%).

Analyses conducted after seeing the data [performed to see *where* statistically significant differences occurred] indicated that patients in the taper and maintenance groups had similar percentages of urine samples testing 'negative' for opioids during the first seven weeks of the trial when all patients were receiving medication (46% vs. 49%), but not during the last seven weeks when patients in the taper group were no longer receiving buprenorphine–naloxone and became less likely to submit samples indicative of abstinence from illicit opioids (33% vs. 64%).

Further analyses conducted after seeing the data indicated that during the first seven weeks of the trial patients in the taper and maintenance groups reported a similar average number of days per week of illicit opioid use (1.08 vs. 0.97 days); in contrast, self-reported illicit opioid use differed during the last seven weeks (1.27 vs. 0.47 days). Patients assigned to the taper group achieved fewer average maximum consecutive weeks of opioid abstinence than those assigned to the maintenance group – the average period of abstinence was three vs. five weeks.

Patients in the taper group were more likely to require protective transfer (16 of 57 vs. 3 of 56) at the end of the first six weeks of the study for 'persistent relapse', defined as more than two consecutive weeks of daily opioid use and urine samples testing 'positive' for opioid use. A study doctor worked with these participants to identify a clinically appropriate treatment plan, for example referral for methadone maintenance therapy, inpatient or intensive outpatient treatment, or for participants assigned to buprenorphine taper, resuming buprenorphine therapy using the initial induction procedure.

In outcomes specific to the taper group, two patients accepted prescriptions for naltrexone, and 16 patients re-initiated buprenorphine therapy.

The authors' conclusions

The buprenorphine taper resulted in fewer urine samples testing 'negative' for opioids, more days of illicit opioid use, fewer weeks of continuous abstinence, and poorer retention in treatment. Very few patients undergoing buprenorphine taper initiated naltrexone therapy or completed treatment, and 28% required reinitiation of buprenorphine therapy owing to relapse after their buprenorphine dose started to taper off.

Based on these findings, medication-assisted withdrawal using a buprenorphine–naloxone taper should be used sparingly (if at all) in primary care for patients who are dependent on prescription opioids; and given the established efficacy of maintenance treatment with methadone and buprenorphine–naloxone, expanded use of maintenance therapy should be the primary response to chronic and relapsing dependence on prescription opioids.

Policies that restrict access to, create financial burdens for, or place arbitrary limits on the duration of maintenance treatment should be reconsidered in the face of evidence that medication tapers lead to relatively poor outcomes (12 13 14 15 16).

FINDINGS COMMENTARY The featured study recruited US patients dependent not on heroin but on opioid medications which can be legally prescribed, and who came for treatment to a primary care clinic specialising in buprenorphine-based treatment of opioid dependence. The key message from the study was "maintain rather than detoxify" in order to prevent illicit opioid use.

For all but a few patients the attempt at withdrawal from buprenorphine ended in treatment drop-out, illicit opioid use, or transfer to maintenance regimen. Just two out of 57 started the naltrexone treatment intended to secure longer lasting opioid abstinence. This was after the trial lost 147 of the 289 patients it assessed before starting the randomised treatments, presumably leaving a set of patients prepared to accept either maintenance or withdrawal.

A number of qualities distinguished the study from real-life practice. Physicians had more experience with buprenorphine and addiction medicine than most primary care providers, on-site drug counselling was available to all participants, something not routinely found in primary care settings, and patient responses to buprenorphine–naloxone (and their preferences for maintenance vs. withdrawal) did not affect treatment allocation. Of the two options available, patient retention and outcomes suggested that maintenance was far more appealing and/or better tolerated, and far more effective in restraining illicit opioid use. After completing the induction and stabilisation period with buprenorphine–naloxone, only 6 of the 57 assigned to receive a taper completed the trial (compared with 37 of the 56 assigned to maintenance) – 34 missed more than a week of medication, 16 met the criteria for protective transfer (including being referred for maintenance therapy instead), and one missed three physician visits.

An Effectiveness Bank drug treatment matrix bite discusses the "great divide" in opiate addiction treatment between approaches which withdraw patients and aim for abstinence from all opiate-type drugs, versus those which maintain them on opiate-type medications (skip to the relevant section). Assessing which of these strategies works best is challenging due to the difficulty of creating a level playing field between the alternatives: suitable patients who opt for withdrawal differ from those not yet ready to relinquish opiate-type drugs, and the two treatments' aims differ so widely that comparing them seems as nonsensical as comparing palliative care for irretrievably ill cancer patients to surgery for those with cleanly excisable tumours.

Yet in everyday practice, people do come to treatment unsure which route to take and their doctors too may be unsure. That uncertainty is likely to be at its greatest among prescription opioid patients who (compared to heroin users) have advantages which might make withdrawal feasible and maintenance an unnecessary prolongation of treatment. The featured trial demonstrated that as with heroin users, withdrawal risks the majority rapidly returning to illicit use of opioids.

Addressing the state of the "opioid epidemic" in 2016, the US Department of Health and Human Services reported that 11.5 million people had misused prescription opioids, 2.1 million of these doing so for the first time (compared with 948,000 having used heroin, 170,000 for the first time), and there were 17,087 deaths attributable to people overdosing on commonly prescribed opioids. In August 2017, the British journal *Prescriber* published a report (freely available at the time of publication) on whether the UK is also "on the verge of a public health crisis". The risk of prescription opioids being diverted to people other than the intended patients is thought to be much lower in the UK than the US, because the oversight of opioid prescribing (and prescribing in general) is much tighter in Britain. However, the misuse or abuse of prescription opioids is difficult to monitor. Some groups are more at risk than others – this includes women ("which is the opposite to what we typically see with traditional illicit substances", says Roz Gittins, chief pharmacist at Addaction, a drug and alcohol treatment charity), people with a history of mental health problems, and people with chronic pain.

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