▶ Unobserved versus observed office buprenorphine/naloxone induction: a pilot randomized clinical trial.

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Having for several hours to medically monitor opiate-addicted patients starting buprenorphine maintenance is a major impediment to spreading the benefits of the treatment, but this first randomised trial suggests that many patients can manage the process safely at home.

Summary In the USA since 2002 primary care practices have been able to treat opioid dependence with buprenorphine and buprenorphine-naloxone (Suboxone), but addiction specialists remain the main prescribers and opioid dependence remains largely untreated. Strategies to engage more general practices in the treatment are urgently needed.

Concern over inducting patients on to buprenorphine is an important barrier, especially over the risk of precipitated withdrawal if buprenorphine is started too soon after the last dose of opiate-type drugs and before the patient is in withdrawal. Also national guidelines recommend new patients are observed and monitored for up to two hours after the first dose, which could significantly increase workload.

Perhaps as a result, some prescribers allow patients to start their buprenorphine treatment unobserved outside the clinic, but this might result in adverse events such as incorrect sublingual tablet administration, precipitated withdrawal, and over-sedation, raising concern about its safety and advisability.

Developing a safe home induction method should encourage more doctors to prescribe and be more convenient for patients. One such method was developed for the featured study and tested on 20 adult patients referred from the Columbia University Medical Center or who responded to adverts. Among other criteria, they had to be free of long-acting opioids such as methadone which complicate induction, and not dependent on alcohol or benzodiazepines. The study was primarily intended to pave the way for a larger trial rather than to test which induction method was best.

Patients were typically male, single, unemployed daily heroin users also suffering other psychiatric problems. Most had a substantial history of imprisonment and arrest, and had been treated before for their addiction. All were treated at the same primary care clinic, where they were randomly allocated to observed or unobserved induction on to buprenorphine-naloxone.

Both groups were told to wait 16 hours after last taking a short-acting opioid before starting buprenorphine, and to take no more than 16mg buprenorphine on the first day. The target daily maintenance dose was usually 12–16mg. Each day they were phoned and asked to rate how they felt on the Subjective Opioid Withdrawal Scale to assess the severity of their withdrawal symptoms, until for two consecutive days they had no appreciable symptoms. Patients were seen at the clinic weekly for the first four weeks and then monthly for brief medical consultations and encouraged but not required to use further psychosocial support.

Where the two groups differed was in whether the first doses were administered under supervision at the primary care surgery, or self-administered at home by the patient. As per national guidelines, for the observed protocol, once withdrawal symptoms had reached the required level medical staff administered 2mg or 4mg of buprenorphine (one or two buprenorphine-naloxone tablets) and more if needed. Patients left the clinic when symptoms had abated.

In the unobserved protocol patients were dispensed their tablets (usually 16 each containing 2mg buprenorphine) at a pharmacy and told to start by taking one or two tablets when their withdrawal symptoms (as assessed by themselves using the Subjective Opioid Withdrawal Scale) reached the same level as applied at the clinic, so long as this was 16 hours after they had last taken heroin or another short-acting opioid.

Main findings

Essentially the different induction methods could not be shown to have made any difference to the success of the treatment.

Successful induction was defined as still being in buprenorphine treatment a week after the initial clinic visit and not suffering withdrawal symptoms. On this basis, whether induction was done at the clinic or by the patient, six in 10 had succeeded. In both groups 3 out of 10 experienced prolonged withdrawal symptoms lasting at least two days. By four weeks, half the patients were still in treatment and four out of 10 were stabilised, not having used illicit opioids for at least two weeks. Seven patients completed the 12-week trial.

One patient among the group conducting their own induction started buprenorphine earlier than instructed and experienced precipitated withdrawal, but stabilised within the first week.

Of the retained patients, under half availed themselves of formal psychosocial therapy. Though unobserved patients took more buprenorphine on the first day (14mg v. 10mg) and on most weeks during the trial, by the end they were taking slightly less.

The authors' conclusions

By adding to the evidence supporting unobserved induction, these findings may help remove an important barrier to widely implementing opioid dependence treatment. However, before unobserved induction can be actively promulgated further confirmation is needed that the approach is no worse than standard clinic-based induction.

The findings indicate comparable safety and effectiveness as measured by induction success, stabilisation, and complication rates. In both groups, 60% successfully inducted. Precipitated withdrawal, a likely concern of many physicians and patients, appears relatively uncommon. Milder prolonged withdrawal was more common, but equally so in both groups.

Using the Subjective Opioid Withdrawal Scale and written instructions to guide at-home induction appears feasible and well received, but the variable initial dose (one or two tablets) and the week-long dosing instructions were confusing to some patients. Future procedures might feature simplified instructions with a standard single first dose and written instructions covering just the first two to three days.

FINDINGS As the authors observed, this study was not large enough to truly test the relative merits of the US standard procedure of observing the first doses at the clinic versus letting the patient take those at home, guided by their self-assessment of their withdrawal severity using the standard Subjective Opioid Withdrawal Scale rating scale. However, other studies have also shown that home induction is

feasible and as effective as clinic-based induction, and almost – but not quite – as safe and free from the risk of precipitated withdrawal.

While medical supervision during induction may still be the ideal (and one advised in relevant UK guidance), these US studies suggest that even some marginalised heroin-injecting patients can induct safely and successfully at home. If as intended this paves the way for appreciably more patients to benefit from primary care-based buprenorphine maintenance, the net result should be to improve the health and prospects of the opiate-addicted population. Further more detailed considerations below.

The induction procedure requires patients to wait to experience a degree of withdrawal discomfort before relieving this with buprenorphine – patients who would previously have found it difficult to resist reacting to the same symptoms by taking illicit opioids. Clearly there might be a temptation (one noted in another report from the same lead author) to opt for relief too soon, either over-estimating the severity of withdrawal or starting medication when withdrawal severity is below the threshold, risking yet more severe precipitated withdrawal.

Precipitated withdrawal happened one out of 10 times in the featured study. However, of the roughly 90% of patients who could be followed up, not one instance was seen in a report on 103 patients who underwent home induction at a New York clinic which only offered this method. Milder symptoms attributed to buprenorphine were noted in five patients, and 11 exceeded the recommended 12mg on day one, reminiscent of the higher doses taken by the home induction patients in the featured study. If induction is done at the clinic, physical signs of withdrawal can be assessed to confirm the patient's reports of how they feel, introduced at one clinic after a case of precipitated withdrawal.

Another clinic in New York moved to offering home induction by mutual agreement between patient and doctor. Patients considered suitable for and who opted for this were as likely to be retained in treatment for 30 days as those with standard clinic-based inductions. Neither induction method was associated with greater difficulties during induction, but one home induction patient (from 51) had to be hospitalised after withholding information about his benzodiazepine use.

Other concerns over home induction must be that patients will inject the medication rather than taking it under the tongue, something the naloxone additive is intended to prevent, but which it does not do so completely. Another is that patients will divert their prescribed medication to the illicit market. The degree to which this happened in the featured study or in New York is unclear. However, in the featured study, even clinic-inducted patients would only be supervised to ensure they took their medication for the first few doses, and then trusted to take it at home, so the extra diversion risk was very slight.

On the basis of recommendations from Britain's National Institute for Health and Clinical Excellence, official UK guidance advises that induction on to buprenorphine should be monitored by a doctor or trained nurse, but also seems to envisage the first dose being supervised by a pharmacist. Relevant guidance specifically for British primary care practices makes no mention of home-based buprenorphine induction, and seems to caution against such procedures when it stipulates that doctors should "see the patient daily if possible" and "ensure frequent review of the patient and supervision of doses, where available, through induction and until stability".

Thanks for their comments on this entry in draft to research author Erik Gunderson of the University of Virginia Health System in the USA. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

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