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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▶ Extended-release naltrexone to prevent opioid relapse in criminal justice offenders.

Lee J.D., Friedmann P.D., Kinlock T.W. et al.

New England Journal of Medicine: 2016, 374, p. 1232–1242.

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Added to basic counselling alone, monthly injections of the opioid-blocking drug naltrexone helped prevent relapse among US offenders with a history of opioid dependence recently released from prison or under criminal justice supervision in the community – findings most applicable to those who prefer opioid-free to opioid-maintenance treatments.

SUMMARY Opioid-use disorder is a chronic condition that has a disproportionate impact on people involved in the US criminal justice system, with relapse and overdose deaths occurring at a high rate after release from prison.

In the US, extended-release naltrexone was approved by the Food and Drug Administration in 2010 for the prevention of relapse to opioid use. Delivered by monthly injection, extended-release naltrexone works by gradually releasing sufficient quantities of naltrexone to block the euphoric effects of opioids.

Opioid maintenance treatments such as methadone and buprenorphine, which provide a legal opiate substitute, have been found effective in prison, jail, and parole settings (1 2 3 4), but have historically been inaccessible, unavailable, or otherwise discouraged among criminal justice clients (5 6 7). As a substance with no known potential to be 'abused' or used illicitly by people other than the intended patients, extended-release naltrexone has gained increasing acceptance in the criminal justice system despite limited data on its effectiveness.

Key points

From summary and commentary

This trial tested the effectiveness of a 24-week course of extended-release naltrexone in preventing opioid relapse among people involved in the US criminal justice system.

Compared with the usual treatment of low intensity, brief counselling, the rate of relapse was lower, but its prevention effects waned after treatment was discontinued.

Extended-release naltrexone may appeal to people who can't access standard opioid maintenance treatments such as methadone and buprenorphine, or who prefer a relapse-prevention medication to taking a legal opiate substitute.

The featured trial tested the effectiveness of a 24-week course of extended-release naltrexone in preventing relapse to opioid use among people involved in the US criminal justice system, comparing it with usual treatment consisting of brief counselling and referral to community treatment programmes. It took place across five sites in north-east America. Participants had a history of opioid dependence, a preference for opioid-free rather than opioid-maintenance treatments, were abstinent from opioids, aged 18 to 60 years, and generally in good health. They lived in the community, and had received a sentence that included supervision (eg, parole, probation, outpatient drug-court programmes, or other court-mandated treatment), or in the previous 12 months had been released from jail or prison, or received a plea-bargain arrangement.

Participants were randomly assigned to receive extended-release naltrexone (153) or usual treatment (155) – the procedure used ensuring balance across the five sites, as well as by sex and status regarding the need for help with withdrawal from opioids.

Trial physicians or nurses administered extended-release naltrexone at a dose of 380 mg by intramuscular injection once every 4 weeks, and provided counselling similar in content to usual treatment participants, focusing on adverse events, the prevention of relapse and overdose, and support for becoming involved in community treatment.

The primary outcome was the amount of time before an 'opioid-relapse event', defined as 10 or more days of opioid use in a 28-day period. This was assessed every two weeks by self-reported opioid use, or by testing urine samples for the presence of opiates. Missed visits and missing data on urine samples were counted as 'positive' for opioid use, meaning participants who left the study added to the number considered relapsed. Follow-ups were undertaken at 27, 52, and 78 weeks after treatment had ended.

Main findings

Participants in the extended-release naltrexone and usual-treatment groups were similar. They averaged 44 years of age and were typically black or Hispanic men on parole or probation. Though during their lifetimes nearly 9 in 10 had used heroin and over 4 in 10 had injected, nearly two-thirds had not used opioids in the previous 30 days and just 9% required help with opioid withdrawal in order to enter the trial.

Scheduled every two weeks during the treatment phase, most of the research assessment visits were attended; participants assigned to extended-release naltrexone attended 79% of the scheduled visits, and those assigned to usual treatment attended 75%. Overall, participants assigned to extended-release naltrexone completed 711 of the 918 planned monthly injections (77%). Seven participants (5%) declined any injections after randomisation; 146 (95%) completed the first injection, 132 (86%) the second, 119 (78%) the third, 111 (73%) the fourth, 100 (65%) the fifth, and 93 (61%) the final injection.

The percentage of participants recording a 'relapse event' was lower among those assigned to extended-release naltrexone than among those assigned to usual treatment (66 participants or 43% vs. 99 participants or 64%), corresponding to an absolute difference in risk of 21%. This finding was consistent with the higher rate of 'negative' urine samples, the lower percentage of days with self-reported opioid use, and the higher percentage of two-week intervals with confirmed abstinence among people assigned to extended-release naltrexone. Time to relapse was also significantly longer in the extended-release naltrexone group than in the usual-treatment group – 10.5 versus five weeks.

However, these impacts did not persist through the follow-ups at weeks 52 and 78 – about six months and 12 months after the treatment phase had ended. There was also no benefit detected of extended-release naltrexone on several important secondary outcomes, including rate of cocaine use, heavy drinking, and injecting drug use.

More participants in the usual-treatment than in the extended-release naltrexone group pursued opioid maintenance treatments during the trial (37% vs. 11%), mainly after they had relapsed and resumed illicit opioid use. No participants reported continuing extended-release naltrexone after the treatment phase; at the time the drug was not widely available in public-sector facilities.

There was no increased risk of overdose events during treatment with extended-release naltrexone or immediately after treatment stopped; indeed, no overdose events were observed among participants assigned to extended-release naltrexone up to the 78 week follow-up, during which time seven overdose events occurred among participants assigned to usual treatment; three were fatal and four were non-fatal.

The authors' conclusions

Among adult offenders with a history of opioid dependence, extended-release naltrexone was associated with a lower rate of relapse to opioid use than the usual treatment of brief counselling and referral to community treatment programmes, however, these prevention effects waned after treatment ended. Testing for opioid use at the later follow-ups revealed that roughly the same numbers in each group could be considered opioid-free after treatment had finished – 49% in the extended-release naltrexone group and 46% in the usual-treatment group at week 52, and 46% in both groups at week 78.

As is the case with any chronic illness, symptoms of opioid-use disorder are more likely to return when effective pharmacotherapy stops, and therefore future research should explore whether

long-term or continuous treatment with extended-release naltrexone would help maintain the short-term benefits observed in this trial and improve longer-term outcomes.

The featured trial had several limitations, one of which was not directly comparing extended-release naltrexone with a standard of opioid maintenance. This comparison has been made in another trial [reportedly completed in January 2017].

Product labels and expert reviews have described a potential overdose risk of extended-release naltrexone *during* treatment when a patient may 'super-dose' opioids to overcome the naltrexone 'block', and *after* treatment when tolerance is low and resumption of opioid use is even more dangerous (8 9). However, there was no evidence of such a risk in this study. No overdose events were observed among participants assigned to extended-release naltrexone up to 78 weeks, during which time seven overdose events occurred among participants assigned to usual treatment.

FINDINGS COMMENTARY Extended-release naltrexone combined with brief counselling was found to be more effective than the usual treatment of brief counselling and referral to community treatment programmes at preventing relapse to opioid use. The study did not compare extended-release naltrexone with a standard opioid maintenance treatment, though another trial involving the lead author of the featured paper did, finding that among a different population of people in community-based inpatient services it was more difficult to initiate patients to extended-release naltrexone than buprenorphine–naloxone – having a knock-on impact on its ability to prevent opioid use or promote abstinence. However, once using the medications, both were equally safe and effective.

Another study comparing extended-release naltrexone with buprenorphine–naloxone (see the entry in the Effectiveness Bank) found that naltrexone was no less effective at retaining patients in treatment, reducing the number of days of injecting and craving for opioids, and reducing the use of heroin, and other illicit drugs. However, as the Effectiveness Bank commentary made clear, the test was of two radically different treatments, intended for different purposes and different types of patients – different not only in the way that they were taken (injected vs. oral), and the frequency of use (roughly monthly vs. daily), but in the pharmacological effects of the drugs themselves:

- Naltrexone promotes abstinence from all opioids by 'forcing' a life free of the effects of these drugs.
- Buprenorphine–naloxone meanwhile provides a legal opiate substitute for patients who want to or feel they have to continue to experience and rely on these drugs, but more safely.

Most participants enrolled in the featured trial had not used opioids in the previous 30 days and had already gone through the process of withdrawal, fitting the typical profile of a naltrexone caseload, rather than a standard substitute prescribing caseload. The authors suggested that extended-release naltrexone may appeal to people who can't access maintenance treatments such as methadone and buprenorphine, or who prefer a relapse-prevention medication. We can also probably add to this patients who are motivated (perhaps due to employment or other pressures) to return to a life without opiate-type drugs, and who have the resources, stability and support to sustain this, as well as unstable patients at very high risk of overdose, but who will not accept or do poorly in substitute prescribing programmes, or people unwilling or unable to accept daily supervised consumption if this is a requirement of being prescribed substitute medications.

Patients in the comparison group (those assigned to usual treatment) were described as receiving similar counselling to naltrexone patients, focusing on adverse events, the prevention of relapse and overdose, and support for community treatment involvement, but presumably minus discussion of the medication side effects and support for treatment participation that naltrexone patients received. Another paper involving the lead author has gone into more detail about what is known as 'medication-management counselling', which does not explicitly incorporate formal therapeutic approaches such as cognitive-behavioural therapy or motivational interviewing, rendering it a relatively unstructured and inexpert counselling, and if delivered every four weeks, a very low intensity counselling.

As a dedicated Effectiveness Bank hot topic shows, while no instant solution, naltrexone injections and implants represent a valuable extension to the range of interventions, meeting the needs of different people depending on their characteristics and circumstances – in particular, those ready for abstinence from opioid drugs. As with other approaches, the social and psychological adjustments needed to stabilise a non-addicted life are likely to take time and require help which goes beyond medication, though this can help create the space for such adjustments.

Last published in 2017, there is no more important document for UK clinicians involved in treating problem drug use than the so-called 'Orange guidelines'. Informing judgements of what constitutes good medical practice, the guidelines state that:
• Among highly motivated patients provided with adequate supervision, naltrexone can help to maintain abstinence.
• Naltrexone should usually be used only after a patient is opioid free (verified by testing for the presence of opioids).
• The impact of naltrexone may be enhanced by additional support from a keyworker or group, allowing service users to discuss any issues related to sustaining abstinence.
• Its effectiveness should be reviewed regularly and if opioid use becomes apparent, discontinuation of naltrexone should be considered.

In an attempt to overcome the problem of poor patient adherence with oral forms of naltrexone (taken daily), work has been undertaken to develop both implant and injectable forms of naltrexone. However, at the time of publication, no such extended-release forms of naltrexone were licensed in the UK or elsewhere in Europe.

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