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.

▶ Title and link for copying ▶ Comment/query to editor ▶ Tweet

▶ Effectiveness of injectable extended-release naltrexone vs daily buprenorphine–naloxone for opioid dependence: A randomized clinical noninferiority trial.

Tanum L., Solli K.K., Latif Z.E. et al.

JAMA Psychiatry: 2017, 74(12), p. 1197–1205.

Unable to obtain a copy by clicking title? Try asking the author for a reprint by adapting this prepared e-mail or by writing to Dr Tanum at lars.tanum@medisin.uio.no. You could also try this alternative source.

Can monthly injections of extended-release naltrexone be considered on a par with the standard daily opioid substitute in Norway for people wanting to maintain abstinence from heroin?

SUMMARY The featured study tested whether among recently withdrawn opiate-dependent patients, injections of extended-release naltrexone were no less effective at maintaining abstinence from heroin and other illicit drugs than the standard treatment for opiate dependence in Norway, substitute prescribing of oral buprenorphine–naloxone on a maintenance basis. If no less effective, the injections offer some advantages which may make them preferable. Lasting up to a month, they block the effects of opiates and are not themselves an 'abusable' drug and do not require frequent attendance at the clinic for supervised consumption of medication.

Participants were recruited through five urban addiction centres in Norway from 1 November 2012 to 10 July 2015. All opioid dependent adults aged 18 to 60 years old who were attending outpatient clinics and medically-supervised withdrawal units were considered for the study. Other forms of drug or alcohol dependence, or serious illnesses and/or their treatments incompatible with the study's treatments, precluded people from participating.

Interviews were conducted with participants at the start of the study, and then again every four weeks. All participants (159) were required to go through the process of withdrawal, before being randomly allocated to receive either extended-release naltrexone hydrochloride (380mg) injected directly into the muscle every four weeks for 12 weeks, or a daily oral dose of buprenorphine–naloxone (a flexible dose of 4–24mg per day). Following the initial phase of treatment (known as 'induction'), participants were also asked to attend standard drug counselling.

The relative safety of the treatments was assessed by comparing reports of adverse events. The primary outcomes of the study were: retention; proportion of urine samples testing negative for illicit opioids; and number of days using heroin and other illicit opioids. Secondary outcomes were: number of days using cannabis, amphetamines, cocaine, benzodiazepines, hallucinogens, and alcohol; number of days of

Key points
From summary and commentary

A novel study testing the relative effectiveness of injections of extended-release naltrexone and a daily combination of oral buprenorphine hydrochloride and naloxone hydrochloride for maintaining abstinence from heroin and other opioids.

Treatment with extended-release naltrexone was found no less effective than buprenorphine–naloxone in terms of 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.

The authors concluded that maintaining short-term abstinence with extended-release naltrexone should be considered an "equal" medication-assisted treatment alternative to buprenorphine-naloxone for opioid-dependent individuals.

injecting drugs; degree of heroin craving; thoughts about heroin; life satisfaction; satisfaction with treatment; and mental health.

Main findings

Adverse events

More adverse events were reported in the extended-release naltrexone group than the buprenorphine–naloxone group (69% vs. 35%). A number of these were related to symptoms of withdrawal such as nausea, chills, shivering, diarrhoea, and sneezing, and again were more frequent among the extended-release naltrexone participants (39% vs. 14%). Six participants from the extended-release naltrexone group and three buprenorphine–naloxone participants reported a serious adverse event. There were no dropouts among these participants – all recovered completely and maintained their study medication. A total of 10 participants discontinued treatment owing to adverse events: four in the extended-release naltrexone group, and six in the buprenorphine–naloxone group.

Primary outcomes

Against all three primary outcomes, extended-release naloxone was found to be "noninferior" to buprenorphine–naloxone [meaning that it wasn't substantially (or it was no more than 20%) worse than buprenorphine–naloxone.] When the researchers assessed whether one treatment was better than the other they found that extended-release naltrexone participants had used heroin significantly less often at all time points and other illicit opioids less often at the four- and eight-week follow-ups.

Retention The average number of days participants received extended-release naltrexone and buprenorphine–naloxone for before discontinuing was similar (69 and 63 days respectively). After 12 weeks, 105 (66%) participants had attended all scheduled follow-up appointments and taken their medication as prescribed, and 53 stopped participating (24 in the extended-release naltrexone group and 29 in the buprenorphine–naloxone group). Of the 80 participants randomly allocated to receive extended-release naltrexone, 56 completed 12 weeks of treatment, while 49 of the 79 receiving buprenorphine–naloxone completed 12 weeks of treatment.

Urine drug tests The proportion of urine samples testing negative for opioids was similar in the extended-release naltrexone and buprenorphine–naloxone groups (average of 80% and 90% respectively).

Use of heroin and other illicit opioids Extended-release naltrexone participants used significantly less heroin at all time points and less of other illicit opioids at weeks four and eight. The average difference in number of days of use of heroin and other illicit opioids was not substantially lower in the extended-release naltrexone group compared with the buprenorphine–naloxone group.

Secondary outcomes

Injecting and use of other drugs There were no significant differences between the treatment groups in the pattern of use of amphetamines, cocaine, alcohol, cannabis, or injecting drugs. However, participants receiving extended-release naltrexone had a significant reduction in days of benzodiazepine use, while the buprenorphine naloxone group remained stable. There were no significant differences between groups at different time points. Hallucinogens were used once or twice by five participants receiving extended-release naltrexone and four receiving buprenorphine naloxone.

Craving and thoughts about heroin At all time points, participants receiving extended-release naltrexone reported significantly less heroin craving and thoughts about heroin than buprenorphine–naloxone participants.

Life satisfaction Life satisfaction was significantly higher among extended-release naltrexone participants at weeks four and eight, but not at week 12.

Satisfaction with treatment Satisfaction with treatment was significantly higher among extended-release naltrexone participants, who were also more likely to recommend their treatment to others compared with buprenorphine–naloxone participants.

Mental health There was no significant difference between the groups in terms of mental health symptoms.

The authors' conclusions

Treatment with extended-release naltrexone was found to be no less effective than buprenorphine–naloxone in 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.

The main clinical implication of the findings was that extended-release naltrexone seems to be as safe as, and no less effective than, buprenorphine–naloxone for patients wanting to maintain abstinence from heroin and other opioids in the short-term, and therefore should be an available treatment option. This applies specifically to opioid-dependent individuals who have recently gone through the process of withdrawal and/or recently been discharged from inpatient treatment or prison, but may also be relevant to the growing number of people addicted to prescription opioids.

FINDINGS COMMENTARY To the authors' knowledge, this was the first study to compare the effectiveness of extended-release naltrexone with a daily combination of buprenorphine and naloxone, the standard opioid medication treatment in Norway (the country the study was conducted in).

Extended-release naltrexone and buprenorphine–naloxone are radically different treatments intended for different purposes and different types of patients. They differ not only in the way that they are 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.

The featured study judged "extended-release naltrexone … as effective as buprenorphine–naloxone in maintaining short-term abstinence from heroin and other illicit substances". The basis for the findings was a "noninferiority trial": a type of trial that seeks to "demonstrate that an experimental treatment is not substantially worse than … [an established] treatment".

Breaking down the meaning and implications of non-inferiority trials, one paper explains that "With continuous improvements in health technologies, standard care, and clinical outcomes, the incremental benefits of newly developed treatments may be only marginal over existing treatments", and so what non-inferiority trials do is (initially) lower the bar for proof of effectiveness in order for new treatments to be brought into the field, established, and further tested. In guidelines for the reporting of such trials, the Consolidated Standards of Reporting Trials (CONSORT) Group acknowledged the frequent use of non-inferiority trials "because of the need to replace standard treatments by other treatments having comparable efficacy but presenting *other advantages*" (emphasis added). The featured paper highlighted some of the "other advantages" of extended-release naltrexone, which included better opportunities for creating a life, routine, and identity (for example through returning to work or education) when not having to meet daily or every second day for supervised intake of medication. This, as the authors pointed out, may help to explain why both satisfaction with treatment and willingness to recommend their treatment to others were significantly higher among extended-release naltrexone participants. Another factor was likely the *novelty* of extended-release naltrexone – versus buprenorphine–naloxone which was widely available in Norway – giving participants the added motivation to try an 'alternative' treatment. Participants were also more typical of a naltrexone caseload than a standard substitute prescribing caseload, as they were all (presumably) abstinent at the start of treatment – having been "discharged from detoxification units, inpatient treatment, or prison" and having gone through the process of withdrawal.

Non-inferiority trials do not feature a control group – a group receiving no intervention or none relevant to the outcomes being assessed. While this falls short of the rigour of 'gold standard' randomised controlled trials, non-inferiority trials are often used when withholding available treatments would have serious outcomes (eg, risk of mortality) for patients. Regardless of the rationale there are implications for the interpretation of findings from non-inferiority trials. The main point is that without a control group it is not possible to assume that any observed effects can be attributed to the treatment of interest (in this case extended-release naltrexone).

Typically in studies which test whether one treatment is superior to another treatment (or no treatment), performing the analysis on an 'intention to treat' sample is the most conservative approach – including all participants who were randomised in the study, regardless of whether they received the treatment or not. However it is not necessarily the most conservative approach in non-inferiority trials as "including dropouts in the analysis tends to bias the results toward [a finding of] equivalence". The recommended approach for non-inferiority trials is to perform intention to treat analysis along with something called 'per-protocol' analysis (including

all patients who satisfactorily complied with the assigned treatment), and to only conclude non-inferiority if *both* analyses produce the same result. The featured paper only reports that an intention to treat analysis was conducted, which the above suggests would not be as cautiously moderate as recommended for this type of (non-inferiority) trial. However, it may be that an intention to treat analysis wasn't conducted anyway – or at least wasn't the only analysis conducted. When the paper described the number of participants included in the analysis (see *Figure 1*), it referred to 56 extended-release naltrexone and 49 buprenorphine–naloxone participants who completed 12 weeks of treatment (ie, the per-protocol sample), not the 80 extended-release naltrexone and 79 buprenorphine–naloxone participants initially randomised (ie, the intention to treat sample). To further complicate matters, the original protocol declared that the data would be analysed with a 'modified intention to treat' sample (a subset of the intention to treat sample, in this case including all randomised patients who received at least one dose of study treatment and who had at least one valid assessment), whereas the more recent protocol, published a year before the study, specified that intention to treat analysis would be performed, and "depending on publication requirements", different analyses would also be conducted.

The clinical interpretation of the findings was that "maintaining short-term opioid abstinence with extended-release naltrexone should be considered an *equal* treatment alternative to buprenorphine–naloxone as medication-assisted treatment for opioid-dependent individuals" (emphasis added). The word *equal* implied equivalence, but the trial wasn't strictly a test of equivalence; it was a test to see that the new treatment wasn't worse than the established treatment "by more than an acceptable amount" (known as the 'margin of difference'). This detail helps in understanding the implications of the findings.

It's recommended that the margin of difference be "prospectively defined" – in other words, decided and declared before the data has been collected and analysed (1 2). In the featured study it was unclear whether the 20% margin was indeed *pre*-set because while it was reported in the 2016 protocol (the year before the featured paper was published), it was not in the original 2012 protocol. Furthermore there was no explanation of how the margin was determined. These traits in reporting are not uncommon in non-inferiority and equivalence trials, leading the CONSORT group to report that "the quality of reports of noninferiority and equivalence trials remains poor". In one review, for example, only about a fifth of 332 non-inferiority and equivalence trials between 1990 to 2000 provided a suitable rationale for the margin of difference, and in another review, almost all 232 reports of noninferiority and equivalence trials specified the margin of difference, but only 24% explained how it was determined (1 2).

A unique study published in the *The Lancet* journal tested what would happen if heroin dependent patients in Malaysia who had been through the process of withdrawal were maintained on a substitute drug, on an opiate-blocking medication, or simply counselled. At the time naltrexone was the main long-term pharmacotherapy and maintenance substitute prescribing was not permitted, but the results – oral naltrexone offered no substantial advantages, but substitute prescribing made a big difference to how long and how many patients were able to live without regular resort to illegal opiates – led to the introduction of methadone prescribing programmes.

Last revised 23 February 2018. First uploaded 31 January 2018

Top 10 most closely related documents on this site. For more try a subject or free text search

STUDY 2015 Opioid treatment at release from jail using extended-release naltrexone: a pilot proof-of-concept randomized effectiveness trial

STUDY 2011 Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial

STUDY 2015 Extended-release naltrexone for alcohol and opioid problems in Missouri parolees and probationers

STUDY 2010 Favorable mortality profile of naltrexone implants for opiate addiction

STUDY 2009 Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial

STUDY 2008 Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: a randomised, double-blind, placebo-controlled trial

HOT TOPIC 2016 Opiate-blocking implants: magic bullet or dangerous experiment?

STUDY 2010 Ultra-rapid opiate detoxification followed by nine months of naltrexone maintenance therapy in Iran

STUDY 2010 The SUMMIT Trial: a field comparison of buprenorphine versus methadone maintenance treatment
STUDY 2010 Naltrexone implants compared to methadone: outcomes six months after prison release