# Extended-release naltrexone versus standard oral naltrexone versus placebo for opioid use disorder: the NEAT three-arm RCT

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# Scientific summary

## The NEAT three-arm RCT

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# Scientific summary

## Background

The Naltrexone Enhanced Addiction Treatment (NEAT) trial was for adults with a diagnosis of opioid use disorder [(OUD) as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition; the most common OUD being illicit heroin use in the UK setting) in the past year, who are detoxified (zero opioid tolerance) and are voluntarily seeking help to stay away from heroin. The primary purpose of the trial was to evaluate the clinical effectiveness and cost-effectiveness of the enhanced naltrexone relapse prevention therapy programme for the treatment of opioid use disorder following National Institute for Health and Care Excellence (NICE) guidelines [NICE. *Drug Misuse: Psychosocial Interventions*. Clinical Guideline (CG)51. London: NICE; 2007]. The NEAT trial was designed to evaluate two formulations of this medication: a 90-day implanted, long-acting form and a short-acting oral tablet form (the active comparator).

## Objectives

### *Primary objectives*

The aim of the NEAT study was to determine the clinical effectiveness and cost-effectiveness of enhanced naltrexone in the treatment of OUD, with the primary objective of answering the following questions:

1. Is extended-release naltrexone treatment more effective than placebo extended-release naltrexone at reducing heroin use?
2. Is extended-release naltrexone is more effective than oral naltrexone at reducing heroin use?
3. What is the relative cost-effectiveness of extended-release naltrexone and oral naltrexone treatment in terms of quality-adjusted life-years?
4. Is extended-release naltrexone more cost-effective than oral naltrexone in terms of quality-adjusted life-years gained?

Objectives 1 and 2 were assessed by urine drug screen (UDS)-verified abstinence from heroin. Objectives 3 and 4 were assessed using health-related quality of life measures.

### *Secondary objectives*

The secondary objectives of NEAT were to:

1. compare treatment retention and medication and psychological intervention adherence rates among the extended-release naltrexone, oral naltrexone and placebo conditions
2. contrast the extended-release naltrexone, oral naltrexone and placebo conditions on quality-of-life indices
3. contrast extended-release naltrexone, oral naltrexone and placebo conditions on:

    - heroin and cocaine craving
    - self-reported opioid, cocaine, amphetamine and benzodiazepine use (with past 48-hour abstinence verified via UDS)
    - alcohol use
    - injection health risk behaviours
    - psychological health (depression and anxiety symptoms)

4. document the safety of extended-release naltrexone and oral naltrexone
5. compare patterns of heroin relapse among the extended-release naltrexone, oral naltrexone and placebo conditions.

## Methods

The NEAT trial was a definitive, two-centre, three-arm, parallel group, placebo-controlled, double-blind, double-dummy, Phase III randomised controlled trial. It evaluated and compared the effectiveness of oral naltrexone with implanted extended-release naltrexone as relapse prevention therapy for OUD. After a literature review and discussion with experts, the team selected 12 weeks as an optimum duration over which to deliver medication, the psychological intervention and the incentivised clinical attendance protocol. Primary and secondary outcomes were assessed after 12 weeks, with follow-up interviews after 16, 24 and 36 weeks.

The trial was double blind. Active and placebo oral medication were produced and encapsulated identically. Active and placebo implant devices were produced and packaged identically. Clinicians and research workers completing baseline, clinic attendance assessments and all follow-ups were blind to group allocation, as were patients and pharmacists. This design ensured that the study had a high level of both treatment integrity (delivery of the treatment as intended) and treatment differentiation (treatment conditions differed from one another in the intended manner). The trial had three groups:

- group A – active extended-release naltrexone and placebo oral naltrexone
- group B – placebo extended-release naltrexone and active oral naltrexone
- group C – placebo extended-release naltrexone and placebo oral naltrexone

## Results

Six patients were recruited and randomised into the NEAT trial. All patients were recruited from the London site by community referral. Three patients were randomised to double placebo, two patients were randomised to active extended-release naltrexone and oral naltrexone placebo, and one patient was allocated to extended-release naltrexone placebo and active oral naltrexone.

Two patients had no positive UDS samples for heroin during the 12-week treatment period, one patient had only one positive UDS sample and the remaining patients had two, six and eight positive UDS samples for heroin. All patients had at least one non-attendance at the clinic (range 1–14). Three patients self-disclosed using heroin during the 12-week treatment period and three patients reported that they did not use heroin during the treatment period. Four of the patients disclosed having a heroin lapse – three of these were during the 12-week treatment period (at 4–5 weeks from randomisation for all three) and one patient disclosed having a heroin lapse at 16 weeks after randomisation (during the follow-up period). Three patients did not take other substances during the 12-week treatment period and three patients were found to have taken other substances (cocaine, methadone, amphetamines, other opioids and benzodiazepine) during this time. Follow-up data on heroin and other substance use were incomplete at the study close.

Three of the patients reported pain at the site of the implant. One patient reported redness, swelling and pain 1 week after the date of the implant, and pus at the site of the implant 2 weeks after implantation. The second of these patients experienced intermittent burning and pain at the implant site, reported at 2 and 3–4 weeks after implantation, and the implant was reported to be unchanged at 5 weeks after implantation. The third of these patients reported swelling at the implant site 3 weeks after implantation. Three of the patients took all their study medication for the duration of the treatment period. Only one patient and one clinician were able to correctly guess the patient's treatment allocation (this happened to be for the same patient). No patients withdrew from the trial.

## Limitations

It is not possible to reach firm conclusions from the observations on the small number of study participants who entered the study. This is a major limitation within this report. However, further understanding of the obstacles encountered and all elements included in the trial design will become available later from the ongoing qualitative investigation of the knowledge, attitudes and behaviour of the six study participants, or potential study participants, all clinical staff and other key individuals. The double-blind, double-dummy trial design was challenging in terms of arrangements to produce the supply of active and placebo treatments and also in terms of introducing this trial design to a treatment field that had not previously encountered it: however, once established, it was broadly understood and acceptable to many potential study participants as well as to staff. Considerable problems were encountered with the stipulated requirement of a validated 'detoxified' status prior to the initiation of the study naltrexone and the requirement for a consent cooling-off period, and also an additional delay awaiting the surgical implant procedure. Ways around these obstacles were developed, to some extent, to mitigate the problems. Difficulty in recruiting study participants on release from prison reduced the ability to apply this treatment to this potentially important patient population.

## Conclusions for practice and research

The bolder trial design (double-blind, double-dummy, placebo-controlled) was challenging to prepare and to explain; however, once the implementation stage was reached, there appeared to be satisfactory acceptability to much of the patient population and clinical staff. However, major clinical and research procedural obstacles, alongside major upheaval to the organisation and delivery of treatment services across England, led to extremely poor levels of actual patient entry into the trial.

## Implications for future research

It remains important to investigate the potential therapeutic value of the opiate antagonist naltrexone, and to compare the established oral form with the new ultra-long-acting depot implant formulations that have been developed, but for which no licensed products exist in Europe and on which research evidence in real-world clinical settings remains insufficient. Despite the small number of study participants recruited up to the point of the decision to close the NEAT trial, some tentative conclusions can be reached, which are relevant to potential future work. The blinding of the active/placebo medications appeared to be good. Self-report was not sufficient to detect instances of heroin use, although subsequent descriptions of lapse events yielded more data. Self-report plus urine analysis gave a fuller picture. Instances of lapsed heroin use were not necessarily followed by full relapse, and future work should consider the lapse–relapse relationship. Smoother navigation of recruitment, consent and procedures will be required if future trials of the same design are to be implemented. The prison release setting is an area that warrants special consideration for this treatment and could wisely be included in planning for a similar future trial.

## Trial registration

This trial is registered as ISRCTN95809946.

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