

Long acting injectable naltrexone is effective and safe for treating alcohol dependence

Garbutt JC, Kranzler HR, O'Malley SS, *et al.* Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *JAMA* 2005;293:1617–25.

Q Is long acting injectable naltrexone an effective and safe treatment for adults with alcohol dependence?

METHODS

 **Design:** Randomised controlled trial.

 **Allocation:** Concealed.

 **Blinding:** Double blind.

 **Follow up period:** Twenty four weeks.

 **Setting:** Twenty four hospitals, clinics, and medical centres in the United States, between February 2002 and September 2003.

 **Patients:** 627 alcohol dependent people, aged 18 years or older. Alcohol dependency was defined by DSM-IV criteria. People with liver failure, levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) three times higher than normal, any medical condition that might affect participation, and pregnant or lactating women were excluded. People with major depression with suicide ideation, psychosis, bipolar disorder, or dependence on benzodiazepines, opiates, or cocaine were also excluded. Participants whose urine samples tested negative for opiates and methadone were randomised.

 **Intervention:** Participants received an intramuscular injection of long acting naltrexone (380 mg (4 ml) or 190 mg (2 ml)), or placebo, every month for six months. All participants received 12 sessions of supportive therapy for addiction, based on the BRENDA (Biopsychosocial, Report, Empathy, Needs, Direct advice, and Assessment) model, from psychologists, nurses, therapists, counsellors or physicians at each study centre. Every four weeks, the injection site was inspected and participants were questioned about the number of standard drinks consumed every day, and any adverse events experienced. The reported number of standard drinks consumed was recorded only if the participant's breath alcohol levels were ≤ 0.02 g/dl.

 **Outcomes:** Event rate of heavy drinking (heavy drinking days/ days "at risk" for heavy drinking; heavy drinking defined as ≥ 5 standard drinks per day for men and ≥ 4 standard drinks per day for women; "at risk" days defined as > 2 drinks per day for men and > 1 drink per day for women); serious adverse events (any medical occurrence that was life threatening, caused death, disability or incapacity, or resulted in or prolonged hospitalisation).

 **Patient follow up:** 401/624 (64%) at six months.

MAIN RESULTS

Long acting, higher dose injectable naltrexone (380 mg), but not lower dose (190 mg), significantly reduced heavy drinking compared with placebo at six months (380 mg: HR 0.75, 95% CI 0.60 to 0.94;

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190 mg: HR 0.83, 95% CI 0.68 to 1.02). There was a similar rate of serious adverse events between treatments (11/205 (5.4%) with 380 mg v 10/210 (4.8%) with 190 mg v 15/209 (7.2%) with placebo; p value not reported).

CONCLUSIONS

Long acting injectable naltrexone reduced heavy drinking compared with placebo in alcohol dependent adults. There was a similar rate of serious adverse events with naltrexone and placebo.

Commentary

The efficacy of naltrexone, an opiate antagonist, in reducing relapse to heavy drinking in people with alcohol dependence has been demonstrated in numerous studies. For people who are most adherent to the prescribed medication the efficacy is more robust. However, in studies performed in frontline treatment programmes with more heterogeneous populations and with fewer exclusion criteria, adherence to the medication regimen has been less than optimal. Adherence is therefore an important factor in determining the feasibility of naltrexone in clinical practice.^{1–3}

The development of a long acting injectable naltrexone to address this problem shows promise. The safety profile and tolerability of the injectable naltrexone, Vivitrex, has been established and is comparable, if not better, than oral administration.⁴ In this large, six month multisite trial by Garbutt *et al.*, monthly administration of Vivitrex reduced heavy drinking episodes in people with alcohol dependence. Retention was high, suggesting the injectable route of administration was acceptable to patients. The 380 mg dose was significantly better than placebo ($p < 0.03$), while the 190 mg dose approached significant difference from placebo ($p < 0.07$).

Clinicians should be aware that certain subgroups of patients might be more or less responsive to the medication. This study showed that being male and abstinent seven days before receiving the first injection were factors that contributed to better outcomes. Although naltrexone was administered in combination with a 12 session low intensity psychosocial therapy, the most improved outcomes are associated with combination cognitive behavioural therapy.^{5,6} However, naltrexone combined with several different psychosocial therapies can reduce relapse to heavy drinking and recidivism in this treatment resistant population. As such, there is a clear indication to integrate this treatment into clinical practice, particularly for alcohol dependent men and those who are not actively using at the initiation of treatment.

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