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# Does naltrexone affect craving in abstinent opioid-dependent patients?

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## ABSTRACT

Naltrexone blocks the opioid receptors that modulate the release of dopamine in the brain reward system and therefore blocks the rewarding effects of heroin and alcohol. It is generally assumed that naltrexone leads to reduction of craving, but few studies have been performed to prove this. The purpose of the present study was to examine the effect of the administration of naltrexone on craving level after rapid opioid detoxification induced by naltrexone. A naturalistic study was carried out in which patients were followed during 10 months after rapid detoxification. Data about abstinence, relapse, and naltrexone use were collected by means of urine specimens. Craving was measured by the visual analogue scale craving, the Obsessive Compulsive Drug Use Scale, and the Desires for Drug Questionnaire. Results showed that patients who relapsed in opioid use experienced obviously more craving than abstinent people. Patients who took naltrexone did not experience significant less craving than those who did not. These results suggest that the use of opioids is associated with increased craving and that abstinence for opioids is associated with less craving, independent of the use of naltrexone. This is in contrast to the general opinion. Because of the naturalistic design of the study, no firm conclusions can be drawn, but the results grounded the needs of an experimental study.

**Keywords** Craving, craving assessment, naltrexone, opioid antagonist, opioid dependence, substance use disorder.

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## INTRODUCTION

Naltrexone is an opioid antagonist and is primarily used in the management of alcohol and opioid dependence (O'Brien 2005). In the last decade, it is also used for the induction of rapid detoxification in opioid-dependent patients. Naltrexone blocks the opioid receptors that modulate the release of dopamine in the reward system and therefore blocks the rewarding effects of heroin and alcohol.

In general, it is assumed that naltrexone leads to reduction of craving. Its use in alcohol dependence has shown to be effective. Patients reported lower craving levels, had fewer relapses, and consumed less alcohol than patients in the placebo group (Davidson *et al.* 1999; Monti *et al.* 1999; Streeton & Whelan 2001; O'Malley *et al.* 2002; Roozen *et al.* 2006). The combination of naltrexone with additional psychosocial treatment is especially effective (Anton *et al.* 1999, 2005; Rubio *et al.* 2002). One aspect of psychosocial treatment is to improve the compliance of the intake of naltrexone (Chick *et al.* 2000). However, some studies found no positive results for naltrexone (Krystal *et al.* 2001; Davidson *et al.* 2004). Overall, reviews confirmed the positive anti-reward effects of naltrexone in decreasing the alcohol consumption, but it does not lead to complete abstinence (Sinclair 2001; Roozen *et al.* 2006).

For opioid dependence, fewer studies have been conducted and findings are less clear. Reviews (Kirchmayer *et al.* 2002; Minozzi *et al.* 2006; Roozen *et al.* 2006) show no satisfactory evidence for preventing relapse by means of maintenance treatment with naltrexone. The acceptability of naltrexone treatment is poor (Bell *et al.* 1999; O'Connor & Fiellin 2000; McGregor *et al.* 2002). Better compliance (Johansson, Berglund & Lindgren 2006) or the use of sustained-release naltrexone (Carreno *et al.*

2003; Comer *et al.* 2006) will probably improve these results. The effect of naltrexone on craving in opioid-dependent patients has been investigated in only a few studies. A decrease in craving was reported in uncontrolled studies (Sideroff, Charuvastra & Jarvik 1978; Judson, Carney & Goldstein 1981). Studies in which naltrexone was compared with placebo yielded inconsistent results. Two found significantly lower craving levels for patients with naltrexone (National Research Council 1978; Lerner *et al.* 1992), one found no differences at all (Krupitsky *et al.* 2006). Krupitsky *et al.* (2004) found only differences between naltrexone and placebo at month 1 and suggested that these differences were accounted for by the use of opioids and not by the effect of naltrexone on opioid receptors. Mirin *et al.* (1976) show an increase in craving during heroin use in unblocked condition and a decrease in craving during detoxification and naltrexone use. During renewed availability of heroin, craving increases again in some patients. This is in line with Judson *et al.* (1981). They found increased craving during opioid use on naltrexone. Previous studies were all carried out with oral naltrexone. Recently, two studies with depot naltrexone shows the same results as above; lower craving levels for naltrexone than placebo (Comer *et al.* 2006); however, in the study of Sullivan, Vosburg & Comer (2006) no control group was used. Grusser *et al.* (2006) showed that naltrexone depot leads to lower craving levels than using an opioid agonist. Compared with healthy control subjects, it was found that craving did not differ significantly from patients with naltrexone at all.

In this paper, we report on the effect of naltrexone at the craving level during a naturalistic study of patients who were followed at 1-, 5- and 10-month follow-up after rapid detoxification induced by naltrexone.

## MATERIALS AND METHODS

### Participants

In this study participants were opioid-dependent patients who participated in the EDOCRA study (De Jong, Laheij & Krabbe 2005). Participants met the following criteria: diagnosed as opioid-dependent according to DSM-IV criteria, previously underwent several unsuccessful attempts to become abstinent, expressed the clear wish to become abstinent, were over 18 years of age, were familiar with the Dutch language, and had at least one non-opioid user in their social network. Exclusion criteria were severe somatic diseases, pregnancy, AIDS, doubts about the patient's willingness to co-operate and contra-indications regarding general anaesthesia. Severe psychiatric disorders, such as acute psychotic episodes and schizophrenia were excluded because of possible complication during the detoxification process. Dependence on other drugs or drug abuse was not an exclusion factor. The Dutch Ethical Assessment Committee for Experimental Investigations on People approved the study.

### Instruments

*Addiction Severity Index*

The Dutch EuropAddiction Severity Index (ASI) (Kokkevi & Hartgers 1995) measures severity of addiction in eight domains (Physical health, Work/education/income, Alcohol, Drugs, Legal problems, Family/social relationships, Psychological/emotional complaints, Gambling) and was used to describe the population.

*Visual analogue scale craving*

By means of a visual analogue scale (VAS) participants were asked to rate craving for drugs on a 100-mm horizontal line from no craving at all (left side) to extremely craving (right side). The result is a score on a continuous scale ranging from 0 to 100.

*Obsessive Compulsive Drug Use Scale*

The Obsessive Compulsive Drug Use Scale (OCDUS) measures the obsessive–compulsive aspects and the experienced general desire to use the drug of choice (general craving) over the previous week. The OCDUS was used according to the psychometric evaluation of Franken, Hendriks & van den Brink (2002). The scale consists of two clear factors, namely 'heroin thoughts and interference' (seven items) and 'desire and control' (four items) with a scale from 1 to 5 (1 = not at all, 2 = a little, 3 = moderately, 4 = quite a bit, 5 = extremely). The total score exists of 13 items with a sum score between 13 and 65.

*Desires for Drug Questionnaire*

The Desires for Drug Questionnaire (DDQ) measures an instant desire, triggered by internal or external cures (instant craving). Franken *et al.* (2002) identified three factors as underlying dimensions, namely 'desire and intention' (seven items), 'negative reinforcement' (four items), and 'control' (two items) with a scale from 1 (totally disagree) to 7 (totally agree). The total score exists of 14 items with a sum score between 14 and 98.

*Urine specimens*

Urine specimens were analysed for naltrexone at the Ziekenhuis Apotheek Laboratorium Venray and for psychoactive substances by the Jellinek laboratory. For the detection of naltrexone, urine samples were enriched in a three-step extraction process and analysed subsequently by high-pressure liquid chromatography with ultraviolet detection. Screening at the Jellinek laboratory was

 

performed on an Olympus AU 600 analyser after immunoassays. The parameters screened for, the specific techniques used and the cut-off values were: opiates: EMIT II, cut-off 300 ng/ml morphine; methadone: CEDIA, cut-off 100 ng/ml EDDP.

### Procedure

After selecting participants according to the inclusion and exclusion criteria (see *Participants*) participants were admitted to an addiction treatment centre. During a 7-day admission all participants underwent rapid detoxification with naltrexone and continued the naltrexone medication. After discharge participants were treated with relapse prevention based on the Community Reinforcement Approach (CRA) in combination with oral naltrexone. CRA in combination with naltrexone proved to be effective in patients with substance-related disorders (Roozen, Kerkhof & van den Brink 2003; Roozen *et al.* 2004). The CRA protocol (Roozen *et al.* 2000) in this study encompassed 23 sessions during 10 months administered by physicians and psychosocial therapists. Main topics in this treatment were the life-style of the patients, compliance for naltrexone (50 mg daily), addictive behaviours, craving, and the occurrence of any adverse event.

This article reports on the craving levels before detoxification (baseline), at discharge and during follow-up. It is a naturalistic study in which the study condition of the participants was derived from urine analysis. Based on the results of urine analysis patients were part of one of three conditions: condition 1, patients who were abstinent and taking naltrexone (OP– NTX+); condition 2, patients who were abstinent without taking naltrexone (OP– NTX–); and condition 3, patients who relapsed in opiate use again (OP+ NTX–). The group sizes of the three conditions changed over time due to the natural course of relapsing in opioid use over time. Urine analyses were carried out at baseline, 1-, 5- and 10-month follow-up. Only patients, whose urine sample was available, were included in the analysis. Craving was assessed through the VAS craving, OCDUS and DDQ at baseline, discharge, and during 1-, 5- and 10-month follow-up.

### Analysis

Differences between the baseline characteristics in the three conditions were analysed for all follow-up measurement by the Pearson $\chi^2$ test (two-tailed) for dichotomous data. Continuous data were compared by the Kruskal–Wallis test because the assumption of normality was not tenable ($P$-value of 0.01 or less considered to indicate statistical significance). ANOVA with Bonferroni *post hoc* comparisons were performed separately for every follow-up measurement at month 1, 5 and 10 with the three conditions as between subject factors and craving as dependent variable. The VAS craving and the total score and subscales of the DDQ and OCDUS were used. Data analyses were performed with SPSS for Windows (12.0.1).

## RESULTS

### Participant characteristics

Participants were 272 opioid-dependent patients (82% men). The mean age of the sample was 35.85 years (SD = 6.4) and participants had been using heroine for an average of 12.0 years (SD = 5.9) and methadone for 7.4 years (SD = 5.7). The mean number of previous detoxifications was 2.9 (SD = 3.7). Most of them were never married (70%), had no (18.1%) or only lower (52.7%) education, and 50.2% had a full-time job. The main demographic characteristics as assessed through the ASI are shown in Table 1. No differences were found between the conditions for baseline characteristics, like severity of addiction, co-consumed substances, personality traits and clinical history. During follow-up measurements 26 patients were excluded from the analysis based on urine analysis pointing out that they used opiates as well as naltrexone (3.8% of the available urine samples).

### Craving

At baseline, all patients were using opioids. According to the VAS craving given by the patients, the baseline mean score was 22.67 (SEM = 1.67). After rapid detoxification (at discharge) all patients were using naltrexone and their mean VAS craving score was 5.57 (SEM = 1.05). After discharge, the condition of patients changed over time, dependent on their urine analysis. Figure 1 shows the VAS craving at admission, discharge, and the follow-ups at month 1, 5 and 10 distinguishing into the three conditions.

In general, analyses of variance showed statistically significant difference between the three conditions for the VAS, the total scores of the DDQ and OCDUS, and most of the subscales, except for the DDQ Negative Reinforcement subscale (month 1) and the DDQ Control subscale (month 1, 5 and 10). *Post hoc* analyses revealed that the two abstinent conditions did not differ significantly, but both conditions differ significantly ($P < 0.05$) with the relapsed condition. See for an overview of the results (Table 2).

## DISCUSSION

This is the first study in which the effect of naltrexone on craving in abstinent opioid-dependent patients was studied in a longitudinal design. The results show that relapsing patients (condition 3) clearly experience more

 

**Table 1** Demographic characteristics of the sample ($n = 272$) (EuropASI).

| *Population characteristics* | | *n* |
|---|---|---|
| Mean age in years (SD) | 35.85 (6.4) | 272 |
| Male (%) | 81.9 | 272 |
| Country of birth (%) | | 234 |
| Europe | 82.9 | |
| Africa | 7.3 | |
| USA | 5.6 | |
| Australia/Oceania | 0.9 | |
| Asia | 3.0 | |
| Other | 0.4 | |
| Marital status (%) | | 260 |
| Single | 70.0 | |
| Married | 14.2 | |
| Divorce/widow | 15.8 | |
| Employment (%) | | 259 |
| Full time | 50.2 | |
| Part time | 10.8 | |
| Unemployed | 39.0 | |
| Education (%) | | 260 |
| None | 18.1 | |
| Lower | 52.7 | |
| Secondary | 20.4 | |
| Higher | 8.8 | |
| Opioid use in years, mean (SD) | | |
| Mean age at first heroine use | 20.83 (5.13) | 251 |
| Mean years heroine | 12.05 (5.86) | 253 |
| Mean age at first methadone use | 24.12 (7.17) | 250 |
| Mean years methadone | 7.40 (5.69) | 252 |
| Opioid use in days, mean (SD) | | |
| Heroin use last 30 days | 18.39 (12.12) | 250 |
| Methadone use last 30 days | 22.82 (10.92) | 252 |
| Other drug use in days, mean (SD) | | |
| Alcohol > 5 glasses last 30 days | 3.59 (8.63) | 239 |
| Cocaine use last 30 days | 4.12 (7.40) | 250 |
| Cannabis use last 30 days | 7.49 (11.56) | 248 |
| Medicine use last 30 days | 6.02 (11.05) | 239 |
| Number of previous detoxifications | 7.89 (7.99) | 254 |
| EuropASI severity, mean (SD) | | |
| Physical health | 1.17 (1.48) | 231 |
| Work, education, income | 2.24 (2.25) | 229 |
| Alcohol | 0.88 (1.65) | 232 |
| Drugs | 6.21 (1.07) | 218 |
| Justice/police | 1.55 (1.91) | 226 |
| Family/social relations | 2.70 (1.84) | 216 |
| Psycho/emotional problems | 2.09 (1.93) | 215 |

EuropASI = EuropAddiction Severity Index.

craving than abstinent patients. This is in accordance with some studies, in which was demonstrated that opioid use causes higher craving levels (Mirin *et al.* 1976; Judson *et al.* 1981; Grusser *et al.* 2006) and craving decreases when patients used naltrexone (Mirin *et al.* 1976; Sideroff *et al.* 1978; Judson *et al.* 1981; Sullivan *et al.* 2006).

We found that abstinent patients taking naltrexone did not experience less craving than people who did not. This is not in the line with what was expected. Abstinent patients taking naltrexone did not experience less craving than people who did not. There are two possible explanations. The first one concentrates on the question why there is no anticraving effect in opioid dependence in comparison with alcohol dependence. Using naltrexone in alcohol dependence the effects of alcohol are not totally blocked. It only attenuates the drug-induced reinstatement, as found in animal studies (Epstein & Preston 2003; De Jong *et al.* 2006). Naltrexone in alcohol dependence will therefore not result in total abstinence, but only in a decrease of alcohol consumption and craving levels (Sinclair 2001; Roozen *et al.* 2006). However, for opioid-dependent patients opioids will have no effect anymore by using naltrexone. As a result of this, no extinguished learning effect will occur to the rewarding opioid effect for opioid-dependent patients, in contrast to alcohol-dependent patients for whom an extinguished learning effect occurs to the rewarding alcohol effects (Sideroff *et al.* 1978).

The second explanation focuses more on the question why there is no difference between the two abstinent conditions. Due to the naturalistic character of the study craving is only measured in neutral environment without exposure to any specific cue provoking craving. It could be that there is a difference between patients with naltrexone and without naltrexone during such cue exposure. However, in animal models it is found that naltrexone does not have effect on cue- and stress-induced reinstatements to use opioids (Shalev, Grimm & Shaham 2002). Finally, the non-existent difference could be explained by the very low craving level during abstinence in both conditions. Naltrexone cannot affect craving if it is not reported anymore.

Other studies found no differences between naltrexone and placebo (Krupitsky *et al.* 2004, 2006). Studies in which a decrease in craving was found did not use control groups (Sideroff *et al.* 1978; Judson *et al.* 1981; Comer *et al.* 2006; Sullivan *et al.* 2006) so it remains doubtful whether these results were due to naltrexone or other parameters, like abstinence. Placebo-controlled trials (National Research Council 1978; Lerner *et al.* 1992) found lower craving levels for naltrexone, but these differences could possibly be accounted for by the use of opioids and not by the effect of naltrexone on opioid receptors.

One of the limitations of the study is that we have no insight in the possibility of selective intake of naltrexone by patients. The choice of the intake of naltrexone could depend on the degree of feeling self-confident in staying

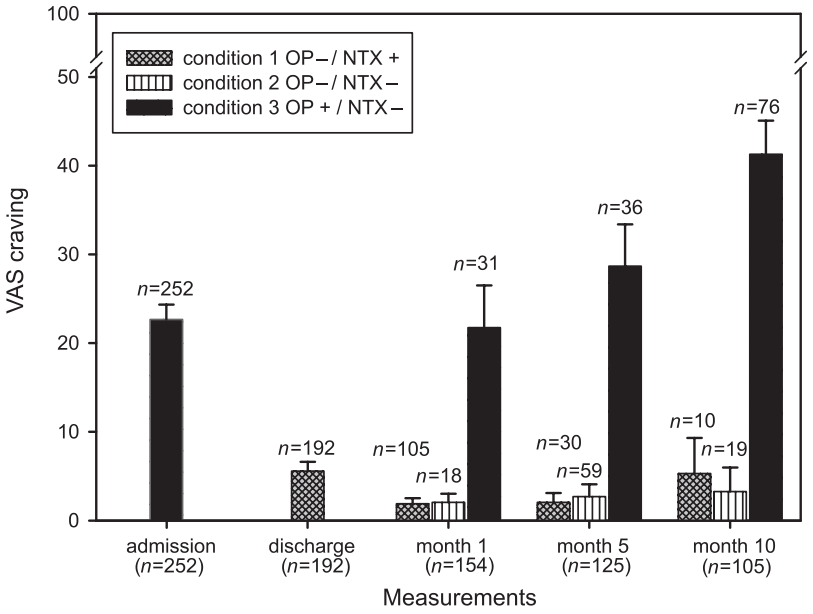


**Figure 1** Visual analogue scale (VAS) craving at admission, discharge and during 10 months of follow-up for three conditions (OP = opioids; NTX = naltrexone; bars show means; error bars show means ± 1.0 SE)

abstinent or because of the presence or absence of positive effects of the naltrexone, due to a genetic vulnerability for the effect of naltrexone (Edenberg & Kranzler 2005; O'Brien 2005). This could have biased our results. In general, the compliance of taking naltrexone is difficult. Failing compliance for taking naltrexone may be more the result of not willing to continue treatment and the absence of agonistic effects like physiological dependence and positive mood state (Cornish *et al.* 1997). Nevertheless, non-compliance only confirms our results that naltrexone has no positive effect on the experienced craving level by abstinent patients. Another limitation is that subjective craving reports could be flattered reduced craving because of social desirable answers of patients. However, in our opinion the differences in craving level between using opioids and not using opioids found here can hardly be fully contributed to social desirability.

Because of the naturalistic design, we are not able to control in advance for variables during the study. We did analyse differences in baseline characteristics and found them not of any influence on the relapse rate or the intake of naltrexone. The impact of co-consumed substances and craving for other drugs on the commitment to the intake of naltrexone and the reported amount of craving during the study cannot be ruled out. We did not find differences in cocaine use during the study between condition 1 and 2.

In conclusion, the results of this naturalistic study show a high association between being abstinence and a low level of craving, independent of the use of naltrexone. The design of the study does not allow us to give a causal explanation, but the results indicate that there is no additional effect of naltrexone on craving levels during abstinence. This is in contrast to what is generally expected. All together these findings should be confirmed in a control-randomized study in which craving levels are to be examined during the intake of naltrexone or placebo. However, such studies are not easy to be executed in practice. In an experimental treatment study one attempt to use an opioid flaws the design, so analyses of craving levels can only be done among subjects who did not try using opioids, a procedure which is comparable with the study of Krupitsky *et al.* (2006). This prevents drawing conclusions about higher craving levels in placebo groups, maybe due to the use of heroin, instead of the effect of naltrexone in experimental groups. Nevertheless, using placebo can prove to be dangerous because of the risk of over dosage in patients in the placebo condition. This raises question about the ethical aspects of such a study. In an experiment in a laboratory setting the effect of cue- and stress-induced exposure in abstinent patients with or without naltrexone could be studied. In this case the question remains if the results can be extrapolated to patients in a treatment setting.

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**Table 2** Means (standard error of means) and ANOVA scores of the craving follow-up measurements by condition 1 [patients who were abstinent and taking naltrexone (OP– NTX+)], condition 2 [patients who were abstinent without taking naltrexone (OP– NTX–)] and condition 3 [patients who relapsed in opiate use again (OP+ NTX–) (d.f. = 2)].

| | *C1:* | | *C2:* | | *C3:* | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *OP– NTX+* | *n* | *OP– NTX–* | *n* | *OP+ NTX–* | *n* | *F* | *P* | *Bonferroni Post hoc* |
| VAS craving | | | | | | | | | |
| F1 | 1.90 (0.63) | 105 | 2.06 (0.96) | 18 | 21.74 (4.75) | 31 | 28.73 | < 0.001 | (C1 = C2) < C3* |
| F5 | 2.05 (1.06) | 59 | 2.70 (1.39) | 30 | 28.67 (4.72) | 36 | 32.44 | < 0.001 | (C1 = C2) < C3* |
| F10 | 5.30 (4.01) | 10 | 3.26 (2.71) | 19 | 41.28 (3.79) | 76 | 17.34 | < 0.001 | (C1 = C2) < C3* |
| DDQ total score | | | | | | | | | |
| F1 | 20.77 (0.98) | 99 | 19.26 (1.87) | 19 | 32.88 (3.33) | 31 | 13.31 | < 0.001 | (C1 = C2) < C3* |
| F5 | 21.03 (1.37) | 60 | 21.93 (2.70) | 30 | 34.97 (2.98) | 35 | 12.18 | < 0.001 | (C1 = C2) < C3* |
| F10 | 23.60 (3.64) | 10 | 19.11 (1.75) | 19 | 42.29 (2.04) | 76 | 19.60 | < 0.001 | (C1 = C2) < C3* |
| DDQ desire and intention | | | | | | | | | |
| F1 | 8.14 (0.30) | 99 | 9.72 (1.35) | 18 | 17.41 (2.33) | 29 | 23.85 | < 0.001 | (C1 = C2) < C3* |
| F5 | 8.72 (0.61) | 60 | 9.37 (1.32) | 30 | 17.46 (1.20) | 35 | 14.79 | < 0.001 | (C1 = C2) < C3* |
| F10 | 9.40 (1.45) | 10 | 7.16 (0.11) | 19 | 22.36 (1.37) | 75 | 20.89 | < 0.001 | (C1 = C2) < C3* |
| DDQ negative reinforcement | | | | | | | | | |
| F1 | 8.01 (0.67) | 99 | 6.63 (1.11) | 19 | 10.91 (1.45) | 30 | 2.90 | 0.058 | – |
| F5 | 7.88 (0.81) | 60 | 7.43 (1.25) | 30 | 11.69 (1.17) | 35 | 4.60 | 0.012 | (C1 = C2) < C3* |
| F10 | 9.70 (2.49) | 10 | 6.63 (0.88) | 19 | 14.25 (0.91) | 76 | 8.82 | < 0.001 | C1 = C2* |
| DDQ control | | | | | | | | | |
| F1 | 4.63 (0.38) | 99 | 3.42 (0.87) | 19 | 6.03 (0.77) | 31 | 2.82 | 0.063 | – |
| F5 | 4.43 (0.49) | 60 | 5.13 (0.77) | 30 | 5.83 (0.63) | 35 | 1.47 | 0.234 | – |
| F10 | 4.50 (1.59) | 10 | 5.32 (1.07) | 19 | 5.97 (0.42) | 76 | 0.71 | 0.493 | – |
| OCDUS total score | | | | | | | | | |
| F1 | 15.46 (0.43) | 100 | 15.94 (1.02) | 18 | 26.88 (2.22) | 32 | 34.09 | < 0.001 | (C1 = C2) < C3* |
| F5 | 15.30 (0.67) | 60 | 15.63 (1.39) | 30 | 27.79 (1.82) | 37 | 32.41 | < 0.001 | (C1 = C2) < C3* |
| F10 | 14.10 (0.98) | 10 | 14.52 (1.00) | 19 | 30.97 (1.31) | 76 | 28.88 | < 0.001 | (C1 = C2) < C3* |
| OCDUS thoughts and interference | | | | | | | | | |
| F1 | 7.90 (0.27) | 100 | 8.22 (0.73) | 18 | 13.04 (1.09) | 32 | 23.03 | < 0.001 | (C1 = C2) < C3* |
| F5 | 7.69 (0.35) | 60 | 8.28 (0.74) | 29 | 13.51 (0.94) | 37 | 25.07 | < 0.001 | (C1 = C2) < C3* |
| F10 | 6.90 (0.41) | 10 | 7.09 (0.66) | 19 | 15.13 (0.71) | 76 | 23.09 | < 0.001 | (C1 = C2) < C3* |
| OCDUS desire and control | | | | | | | | | |
| F1 | 4.74 (0.14) | 100 | 5.11 (0.39) | 18 | 9.62 (0.82) | 32 | 47.86 | < 0.001 | (C1 = C2) < C3* |
| F5 | 5.15 (0.27) | 59 | 5.10 (0.55) | 30 | 9.68 (0.71) | 36 | 28.27 | < 0.001 | (C1 = C2) < C3* |
| F10 | 4.70 (0.40) | 10 | 4.63 (0.32) | 19 | 10.57 (0.48) | 76 | 27.93 | < 0.001 | (C1 = C2) < C3* |

C1 = condition 1; C2 = condition 2; C3 = condition 3; DDQ = Desires for Drug Questionnaire; F1 = follow-up month 1; F5 = follow-up month 5; F10 = follow-up month 10; OCDUS = Obsessive Compulsive Drug Use Scale; OP = opioids; NTX = naltrexone. *C1 = C2 (n.s. at $P < 0.1$); C1 < C3 and C2 < C3 (at $P < 0.05$).

## References


Anton RF, Moak DH, Latham P, Waid LR, Myrick H, Voronin K, Thevos A, Wang W, Woolson R (2005) Naltrexone combined with either cognitive behavioral or motivational enhancement therapy for alcohol dependence. J Clin Psychopharmacol 25:349–357.

Anton RF, Moak DH, Waid LR, Latham PK, Malcolm RJ, Dias JK (1999) Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial. Am J Psychiatry 156:1758–1764.

Bell JR, Young MR, Masterman SC, Morris A, Mattick RP, Bammer G (1999) A pilot study of naltrexone-accelerated detoxification in opioid dependence. Med J Aust 171:26–30.

Carreno JE, Alvarez CE, Narciso GI, Bascaran MT, Diaz M, Bobes J (2003) Maintenance treatment with depot opioid antagonists in subcutaneous implants: an alternative in the treatment of opioid dependence. Addict Biol 8:429–438.

Chick J, Anton R, Checinski K, Croop R, Drummond DC, Farmer R, Labriola D, Marshall J, Moncrieff J, Morgan MY, Peters T, Ritson B (2000) A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. Alcohol Alcohol 35:587–593.

Comer SD, Sullivan MA, Yu E, Rothenberg JL, Kleber HD, Kampman K, Dackis C, O'Brien CP (2006) Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. Arch Gen Psychiatry 63:210–218.

Cornish JW, Metzger D, Woody GE, Wilson D, McLellan AT, Vandergrift B, O'Brien CP (1997) Naltrexone pharmacotherapy for opioid dependent federal probationers. J Subst Abuse Treat 14:529–534.

Davidson D, Palfai T, Bird C, Swift R (1999) Effects of naltrexone on alcohol self-administration in heavy drinkers. Alcohol Clin Exp Res 23:195–203.

Davidson D, Saha C, Scifres S, Fyffe J, O'Connor S, Selzer C (2004) Naltrexone and brief counseling to reduce heavy drinking in hazardous drinkers. Addict Behav 29:1253–1258.

De Jong CAJ, Laheij RJ, Krabbe PF (2005) General anaesthesia does not improve outcome in opioid antagonist detoxification treatment: a randomized controlled trial. Addiction 100:206–215.

De Jong CAJ, Schellekens AFA, Ellenbroek B, Franke B, Verkes R-J (2006) The Course of Addiction. Neurobiological Predictors of Chronicity. Den Haag: ZonMw, programma Verslaving.

Edenberg HJ, Kranzler HR (2005) The contribution of genetics to addiction therapy approaches. Pharmacol Ther 108:86–93.

Epstein DH, Preston KL (2003) The reinstatement model and relapse prevention: a clinical perspective. Psychopharmacology (Berl) 168:31–41.

Franken IH, Hendriks VM, van den Brink W (2002) Initial validation of two opiate craving questionnaires the obsessive compulsive drug use scale and the desires for drug questionnaire. Addict Behav 27:675–685.

Grusser SM, Thalemann CN, Platz W, Golz J, Partecke G (2006) A new approach to preventing relapse in opiate addicts: a psychometric evaluation. Biol Psychol 71:231–235.

Johansson BA, Berglund M, Lindgren A (2006) Efficacy of maintenance treatment with naltrexone for opioid dependence: a meta-analytical review. Addiction 101:491–503.

Judson BA, Carney TM, Goldstein A (1981) Naltrexone treatment of heroin addiction: efficacy and safety in a double-blind dosage comparison. Drug Alcohol Depend 7:325–346.

Kirchmayer U, Davoli M, Verster AD, Amato L, Ferri A, Perucci CA (2002) A systematic review on the efficacy of naltrexone maintenance treatment in opioid dependence. Addiction 97:1241–1249.

Kokkevi A, Hartgers C (1995) EuropASI: European adaptation of a multidimensional assessment instrument for drug and alcohol dependence. Eur Addict Res 4:208–211.

Krupitsky EM, Zvartau EE, Masalov DV, Tsoi MV, Burakov AM, Egorova VY, Didenko TY, Romanova TN, Ivanova EB, Bespalov AY, Verbitskaya EV, Neznanov NG, Grinenko AY, O'Brien CP, Woody GE (2004) Naltrexone for heroin dependence treatment in St. Petersburg, Russia. J Subst Abuse Treat 26:285–294.

Krupitsky EM, Zvartau EE, Masalov DV, Tsoy MV, Burakov AM, Egorova VY, Didenko TY, Romanova TN, Ivanova EB, Bespalov AY, Verbitskaya EV, Neznanov NG, Grinenko AY, O'Brien CP, Woody GE (2006) Naltrexone with or without fluoxetine for preventing relapse to heroin addiction in St. Petersburg, Russia. J Subst Abuse Treat 31:319–328.

Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA (2001) Naltrexone in the treatment of alcohol dependence. N Engl J Med 345:1734–1739.

Lerner A, Sigal M, Bacalu A, Shiff R, Burganski I, Gelkopf M (1992) A naltrexone double blind placebo controlled study in Israel. Isr J Psychiatry Relat Sci 29:36–43.

McGregor C, Ali R, White JM, Thomas P, Gowing L (2002) A comparison of antagonist-precipitated withdrawal under anesthesia to standard inpatient withdrawal as a precursor to maintenance naltrexone treatment in heroin users: outcomes at 6 and 12 months. Drug Alcohol Depend 68:5–14.

Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A (2006) Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev (1):CD001333.

Mirin SM, Meyer RE, McNamee HB, McDougle M (1976) Psychopathology, craving, and mood during heroin acquisition: an experimental study. Int J Addict 11:525–544.

Monti PM, Rohsenow DJ, Hutchison KE, Swift RM, Mueller TI, Colby SM, Brown RA, Gulliver SB, Gordon A, Abrams DB (1999) Naltrexone's effect on cue-elicited craving among alcoholics in treatment. Alcohol Clin Exp Res 23:1386–1394.

National Research Council (1978) Clinical evaluation of naltrexone treatment of opiate-dependent individuals. Report of the National Research Council Committee on Clinical Evaluation of Narcotic Antagonists. Arch Gen Psychiatry 35:335–340.

O'Brien CP (2005) Anticraving medications for relapse prevention: a possible new class of psychoactive medications. Am J Psychiatry 162:1423–1431.

O'Connor PG, Fiellin DA (2000) Pharmacologic treatment of heroin-dependent patients. Ann Intern Med 133:40–54.

O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek MJ (2002) Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo-pituitary-adrenocortical axis. Psychopharmacology (Berl) 160:19–29.

Roozen HG, Boulogne JJ, van Tulder MW, van den Brink W, De Jong CA, Kerkhof AJ (2004) A systematic review of the effectiveness of the community reinforcement approach in alcohol, cocaine and opioid addiction. Drug Alcohol Depend 74:1–13.

Roozen HG, De Jong CAJ, Kerkhof AJFM, Geerlings PJ, Schippers GM (2000) EDOCRA: Manual CRA [EDOCRA: Handleiding CRA]. Sint-Oedenrode: Novadic.

Roozen HG, de Waart R, van der Windt DA, van den Brink W, de Jong CA, Kerkhof AJ (2006) A systematic review of the effectiveness of naltrexone in the maintenance treatment of opioid and alcohol dependence. Eur Neuropsychopharmacol 16: 311–323.

Roozen HG, Kerkhof AJ, van den Brink W (2003) Experiences with an outpatient relapse program (community reinforcement approach) combined with naltrexone in the treatment of opioid-dependence: effect on addictive behaviors and the predictive value of psychiatric comorbidity. Eur Addict Res 9:53–58.

Rubio G, Manzanares J, Lopez-Munoz F, Alamo C, Ponce G, Jimenez-Arriero MA, Palomo T (2002) Naltrexone improves outcome of a controlled drinking program. J Subst Abuse Treat 23:361–366.

Shalev U, Grimm JW, Shaham Y (2002) Neurobiology of relapse to heroin and cocaine seeking: a review. Pharmacol Rev 54:1–42.

Sideroff SI, Charuvastra VC, Jarvik ME (1978) Craving in heroin addicts maintained on the opiate antagonist naltrexone. Am J Drug Alcohol Abuse 5:415–423.

Sinclair JD (2001) Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism. Alcohol Alcohol 36:2–10.

Streeton C, Whelan G (2001) Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials. Alcohol Alcohol 36:544–552.

Sullivan MA, Vosburg SK, Comer SD (2006) Depot naltrexone: antagonism of the reinforcing, subjective, and physiological effects of heroin. Psychopharmacology (Berl) 189:37–46.

 