Effectiveness of Low-Dose Naltrexone in the Post-Detoxification Treatment of Opioid Dependence

Paolo Mannelli, MD, Ashwin A. Patkar, MD,* Kathleen Peindl, PhD,* Heather W. Murray, PhD,† Li-Tzy Wu, ScD,* and Robert Hubbard, PhD**

Background: The clinical use of naltrexone (NTX) in the treatment of opioid dependence has been limited because of poor compliance and inconsistent outcomes. In particular, the therapeutic benefit of extended treatment with NTX after opioid detoxification is unclear. The present study evaluated whether the augmentation with low-dose NTX during the post-detoxification treatment of opioid dependence would improve outcomes.

Methods: In an open-label naturalistic design, 435 opioid-dependent patients who had completed inpatient detoxification were offered the choice of entering 1 of the 2 outpatient treatment arms: clonidine extended treatment (CET) (clonidine + psychosocial treatment), or enhanced extended treatment (EET) (oral NTX [1–10 mg/d] + CET) for 21 days. The primary outcome measure was retention in treatment. Secondary outcomes included abstinence from opioids, dropouts, and adherence to postdischarge care.

Results: One hundred sixty-two patients (37.2%) accepted EET. Subjects receiving EET stayed longer in the program ($F = 64.4$; $P = 0.000$), were less likely to drop out, used less opioids, and followed through with referral to long-term outpatient treatment in a higher number, compared with patients in the CET arm ($P = 0.000$ in each case). The NTX + clonidine combination was safe and well tolerated.

Conclusions: This preliminary study indicates the potential benefit of augmentation with low-dose NTX to improve outcomes after opioid detoxification for a preferred group of patients. Randomized controlled trials are necessary to further evaluate the role of low-dose NTX in the outpatient treatment of opioid dependence.

(*J Clin Psychopharmacol* 2007;27:468–474)

The clinical use of narcotic antagonists in the treatment of opioid dependence has been limited by scarce adherence and inconsistent treatment outcomes.[1,2] Naltrexone (NTX) has been frequently used in the treatment of opioid withdrawal.[3,4] However, its effectiveness to maintain abstinence seems limited, and only selected populations of highly motivated individuals benefit from its administration.[5–7] Moreover, reports on adverse events (AEs) observed in patients receiving NTX[8,9] and ambivalent attitudes toward opiate antagonists among patients and substance abuse professionals[10–12] have raised concern about the clinical acceptability of an antagonist to treat opioid dependence. Despite the limitations, NTX is neither a controlled substance, nor it displays abuse potential and may increase treatment options for patients.

Efforts to improve acceptance of NTX in outpatient settings have included the adoption of specific behavioral interventions[13,14] and the use of opiate antagonists in detoxification protocols.[15] However, these options are not readily available, and methadone-assisted detoxification remains the most common or the only treatment offered in community-based opioid programs.[16]

An alternative approach to broaden the use of NTX is reduction in dose. The customary dosage of 50 mg/d NTX has been associated with adverse neuropsychiatric and gastrointestinal side effects, such as dysphoria, nausea, and abdominal pain in a seemingly dose-dependent fashion.[17–20] As opposed to the full-blockade obtained with 25 to 50 mg/d, the partial occupation of opioid receptors provided by lower NTX doses[21] may attenuate the effects of opioids that are intermittently abused by many patients after detoxification.[22] This may in turn prevent or delay the onset of neuroadaptation that favors sensitization and full relapse into abuse.[23,24]

The use of low-dose NTX has been associated with increased analgesia and reduced dependence and withdrawal, either in experimental settings[25–27] or during clinical trials and detoxification.[28–30] A range of NTX doses have been used in clinical investigations of relapse prevention. In general, daily doses of 10 to 25 mg of NTX have demonstrated comparable effectiveness with 50 mg,[31–33] whereas quantities of less than 1 mg/d showed low effectiveness and received scarce acceptance among patients.[34] The use of NTX doses between 1 and 10 mg has received little attention, and only partial indications are associated with the efficacy of sustained-release formulations in maintaining abstinence.[35–37] The daily quantity of NTX released in this case fluctuates between 5 and 10 mg, but oral administration of similar doses would produce different plasma concentrations, with a lower 24-hour exposure to the drug.[38] Considering also that the minimum effective

*Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC; †Brown University, Providence, RI.

Received July 20, 2006; accepted after revision July 7, 2007.

This research was supported in part by grant DA15469 from the National Institute on Drug Abuse to P. Mannelli.

Portions of this study were presented at the 158th Annual Meeting of the American Psychiatric Association, May 21–26, 2005.

Address correspondence and reprint requests to Paolo Mannelli, MD, Duke University Medical Center, 2218 Elder St 2B, Suite 123, Durham, NC 27705. E-mail: Paolo.Mannelli@duke.edu.

ISSN: 0271-0749/07/2705-0468

DOI: 10.1097/jcp.0b013e31814e5e9d

therapeutic plasma concentration of NTX is not well understood,[38] more information has to be gathered on the clinical use of low-dose NTX for the treatment of opioid dependence, particularly in the case of the dose range of 1 to 10 mg after detoxification.

Although treatment with opioid agonist and partial agonist (methadone and buprenorphine) is clearly effective in reducing relapse,[39] not all patients are appropriate or willing to undergo substitution therapy. Therefore, alternative treatment options are needed at the time of opioid discontinuation. Although inpatient opioid detoxification is associated with higher completion rates,[40] the inpatient-outpatient transition is difficult. Early relapse is common and can be reduced by engaging subjects in continuing care activities after discharge.[41,42] Unfortunately, adherence with nonmethadone, outpatient aftercare is often poor, averaging 14% in a national survey of drug dependence treatment programs.[43] This leads to return to detoxification, a "revolving door" phenomenon that constitutes both a clinical challenge and an economic burden in the treatment of opioid dependence.[44] If low doses of NTX can be safely administered in continuity with opioid detoxification and contribute to reduce chances of resuming abuse, this may help compliance and also delay the need for a new detoxification.[12,45] The objective of this study was to evaluate whether augmentation with NTX 1 to 10 mg/d would be safe and beneficial during post-detoxification outpatient treatment of opioid dependence.

MATERIALS AND METHODS

Subjects and Treatments

Study subjects were recruited among opioid-dependent patients treated at a publicly funded hospital in Philadelphia with inpatient and outpatient treatment facilities.

Eligible subjects included men and women aged 18 to 65 years who had completed inpatient methadone + clonidine detoxification (4–6 days) within the previous 24 hours. Patients were accepted if they met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for opioid dependence (American Psychiatric Association, 1994) and were able to understand and comply with the treatment regimen. Exclusion criteria were history of hypersensitivity to NTX; dependence on substances other than opioids; *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnoses of psychotic disorder, major depression, or bipolar disorder, presence of suicidal risk, or serious or unstable medical disorder. Participating women were required to use approved methods of contraception.

Design

This was a 3-week open-label naturalistic trial evaluating the clinical use and safety of enhanced extended treatment (EET; oral NTX [1–10 mg/d] + clonidine and psychosocial treatment) in opioid-dependent patients after inpatient detoxification, compared with extended clonidine treatment (CET; clonidine + psychosocial treatment) that continued the clonidine treatment offered during detoxification. Subjects were given the possibility to choose between treatments to parallel clinical practice in which many patients may not accept the recommendation to try NTX.[10]

Study Interventions and Procedures

The study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Thomas Jefferson University, Philadelphia. Written informed consent was obtained from all subjects before performing any protocol. Prospective subjects were told that clonidine is used to treat opioid withdrawal discomfort that is frequently associated with relapse.[15] Such discomfort may lead to treatment discontinuation among opioid-dependent patients and the study was intended to understand whether adding the specified quantity of NTX would help patients be more comfortable and remain in treatment, before continuing with long-term outpatient care. As an alternative to study, individuals were directly referred to long-term outpatient treatment. No treatment program was locally available that administered NTX after the study. Screening procedures included a review of clinical history. Patients in the study were offered concomitant psychosocial treatment combining counseling sessions (6 h/wk) and case management. Individual and group therapy sessions focused primarily on motivation enhancement, problem solving, and relapse prevention.[46,47] Enrolled patients received medications under outpatient staff supervision daily, between 9 and 11 AM. Subjects were offered the choice of EET or CET treatment. The CET pharmacological protocol consisted of the application of a clonidine transdermal patch (Catapres-TTS-2 releasing an average 0.2 mg/d for approximately 1 week) on Days 1, 7, and 15, with final removal on Day 21. Concomitant oral clonidine (Catapres) was administered as follows: Day 1, 0.4 mg; Day 2, 0.6 mg; Days 3 to 5, 0.5 mg; Days 6 to 8, 0.4 mg; Days 9 to 14, 0.2 mg; and Days 15 to 21, 0.1 mg.

The EET schedule added low-dose NTX to clonidine, administered with the same modalities as in the CET protocol. Naltrexone hydrochloride UPS powder (Medisca Inc) was compounded into 1-, 3-, and 5-mg capsules at the hospital pharmacy. The NTX dose escalation schedule was as follows: Day 1, 1 mg; Day 2, 2 mg; Day 3, 3 mg; Days 4 to 6, 5 mg; Days 7 to 21, 10 mg. If patients reported opioid use in the previous 24 hours, or a positive urine drug screen (UDS) for opioids was detected, the subsequent NTX dose was 1 mg, and the dose titration was restarted.

Adjuvant drugs were available for symptomatic treatment of residual opioid withdrawal, such as bone/muscle pain, abdominal cramps, nausea, diarrhea, and anxiety. Palliative medications were administered as needed and as a "take home" option in both CET and EET treatment groups (range of milligrams per day allowed: hydroxyzine 50–100, ibuprofen 400–800, baclofen 5–10, and loperamide 2–4).

Assessments

Psychosocial and behavioral evaluations were performed at admission. The Government Performance Results Act[48] is a structured interview that is designed to assess the status of the patient in the last 30 days in several areas of functioning, including drug and alcohol use, family and living conditions, education, employment, and mental and

physical health problems during the previous 30 days. The Symptom Check List[49] is a 90-item (each scored 0–4) inventory of a wide variety of psychophysical symptoms and complaints. The 21-item (each scored 0–3) Beck Depression Inventory[50] is commonly used as a self-reported measure of depression. Subjects' readiness for substance abuse treatment was evaluated using a modified version of the Recovery Attitude and Treatment Evaluator–Research scale, a structured interview including 17 questions, each scoring 1 to 6.[51] A withdrawal scale modified from Handelsman et al[52] was used to evaluate 13 withdrawal symptoms, each self-rated on a 0 to 3 range of intensity at admission and then daily during the first week, along with vital signs. Urinalyses (UDS) for drugs of abuse (opioids, cocaine, cannabis, and amphetamine) were obtained at admission and once a week thereafter.

Outcome Measures

The primary outcome was retention in treatment, as defined by days in treatment. Attendance was recorded as duration from date of first visit to date of last visit, before referral.

Secondary measures were drug use, proportion of dropouts, attendance to counseling, and adherence to post-discharge care, according to the following definitions: (1) UDS—UDS were obtained for all subjects randomly every week during the treatment period. The number of negative UDS for opioids and other drugs of abuse were recorded, excluding the admission UDS. Patients should provide 2 consecutive clean samples for opioids before discharge and referral. (2) Dropouts—these were defined as individuals who stopped attending the treatment program for at least 1 week during the trial. (3) Number of treatment sessions—the total number of group and individual sessions attended by the patient was calculated. This reflects participation in the treatment process. (4) Adherence with postdischarge care—to meet the criteria for treatment continuation, the subjects who completed the treatment program had to follow through with the suggested referral to long-term drug-free treatment.

Statistical Analyses

Demographic characteristics, drug use, and treatment outcomes were compared between patients in EET and CET groups. χ^2 tests were used for differences regarding dichotomous variables. Univariate analysis of variance (ANOVA) with or without repeated measure, or analysis of covariance (ANCOVA) using sex and ethnicity as covariates were performed on continuous variables. A linear regression model was produced to evaluate the role of NTX in predicting treatment outcome. Finally, we calculated an additional measure of treatment effect, the "number needed to treat" (NNT), which is considered useful in the interpretation of clinical trial data for treatment decision making.[53] In this case, the NNT is the estimated number of patients who need to be treated in the EET and CET groups for 1 additional patient to positively respond to NTX, according to the criteria of staying in treatment and continuing with postdischarge care. An intent-to-treat analysis was performed, examining all patients enrolled in the trial. The study was sufficiently powered, based on the effect size observed in clinical trials of oral NTX.[54]

RESULTS

Subjects

Four hundred sixty-six of 620 eligible patients were screened, and 435 were enrolled over a period of 21 months. Baseline sociodemographic and clinical features of the enrolled patients are summarized in Table 1.

One hundred sixty-two of the 435 subjects (37.2%) accepted pharmacological treatment with NTX (EET group), whereas 273 (62.8%) opted for clonidine and adjuvant medications alone (CET group). Less than 6% of the patients had previously received NTX treatment (EET = 10; CET = 14; $\chi^2 = 0.21$; P, not significant). Groups did not differ in terms of demographic, severity of drug use, and psychopathology at admission. Almost 70% of the patients were men, and approximately 30% of them were members of an ethnic

TABLE 1. Baseline Sociodemographic and Clinical Characteristics of Opioid-Dependent Subjects (n = 435)

	EET = 162 (SD)	CET = 273 (SD)
Demographics		
Age	32.94 (9.09)	32.76 (9.37)
Hispanic, African American	28%	34%
Male	68.5%	66.8%
Years of education	11.10 (1.89)	10.83 (1.78)
Unemployed	79.2%	80.8%
Drug use		
Years of opioid use	12.3 (4.01)	13.1 (5.93)
Opioid use in last 30 days	21.8 (8.10)	20.64 (8.54)
Alcohol use in last 30 days	43.7%	44.2%
Other substances*	67.2%	67.7%
Previous detoxifications	3.13 (1.92)	3.84 (0.95)
Baseline measures		
Positive urine opioids	47.8%	46.9%
Positive urine other drugs	38.8%	36.6%
Withdrawal score (0–39)	14.27 (4.02)	14.52 (3.93)
Beck Depression Inventory (0–63)	13.79 (6.23)	13.95 (6.58)
SCL-90-R subscores		
Somatization (0–48)	2.32 (0.86)	1.95 (0.82)
Anxiety (0–40)	1.22 (0.98)	1.14 (0.92)
Hostility (0–24)	0.95 (0.94)	0.93 (0.89)
Psychoticism (0–40)	0.74 (0.76)	0.76 (0.77)
RAATE-R subscores		
Resistance to treatment (7–42)	18.32 (6.72)	17.28 (7.11)
Resistance to continued to care (2–12)	8.64 (2.25)	9.11 (3.01)

All comparisons not significant; 1-way ANOVA: F ranging from 0.3 to 1.2, degrees of freedom ranging from 1230 to 1435 for; χ^2 ranging from 0.20 to 3.40, degrees of freedom = 1.

*Including cocaine, marijuana, amphetamine.

RAATE-R indicates Recovery Attitude and Treatment Evaluator–Research scale; SCL-90-R, Symptom Check List.

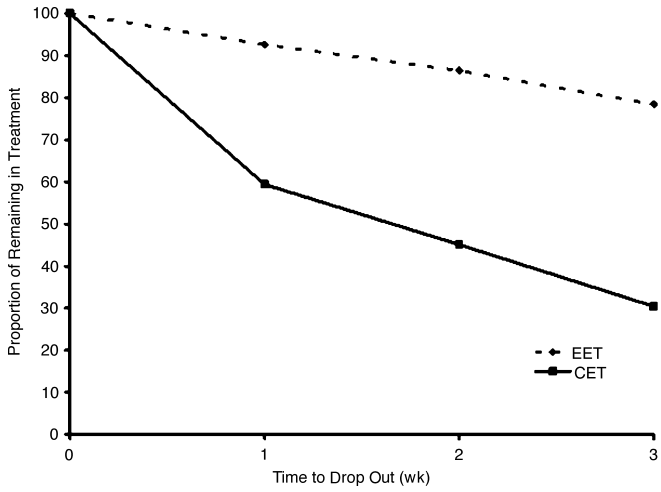

FIGURE 1. Time until discontinuation among patients treated in the EET and CET groups. More subjects dropped out in the CET group during the trial period. Kaplan-Meier survival analysis. χ^2_1 (Breslow) = 143.96; P = 0.000.

minority group (African American and Hispanic). A high proportion of patients in both groups was unemployed (around 80%), most of them reported concomitant use of alcohol (43%) or other substances (67%) and more than 20 days of average opioid use in the previous month. When withdrawal symptom scores were evaluated, the 2 groups again seemed to be similar. The relatively low withdrawal scores noted might be consistent with recent administration of methadone and clonidine during the inpatient detoxification or active opioid use in the 24 hours elapsed between discharge from detoxification and admission to outpatient treatment. In fact, almost half of the patients in both groups had positive UDS for heroin metabolites at the time of pretreatment evaluation, indicating a high rate of relapse to opioid use within 24 hours of inpatient detoxification.

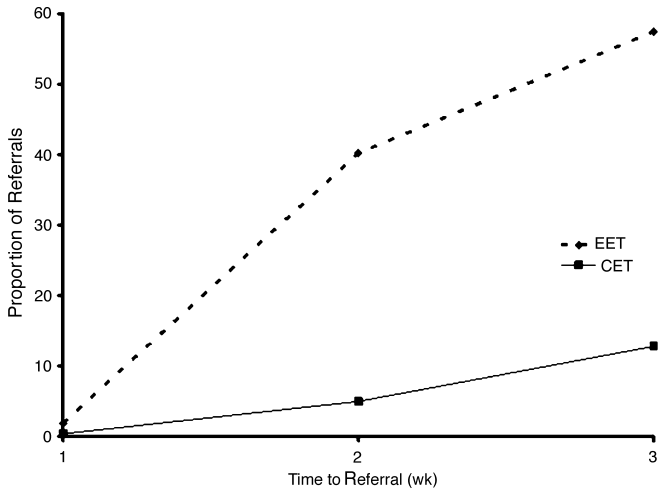

FIGURE 2. Time to long-term outpatient treatment referral in the EET and CET groups. More patients in the EET group followed through with a referral. Kaplan-Meier survival analysis. χ^2_1 (Breslow) = 163.62; P = 0.000.

Subjects were admitted to study between 18 and 36 hours (median, 21 hours) after discharge from detoxification.

Treatment Outcome

When the outcomes of the 3-week trial were compared controlling for sex and ethnicity, patients from the EET group showed better retention in the program (1-way ANCOVA, $F_{1,431}$ = 56.4; P = 0.000) and attended more group and individual sessions (1-way ANCOVA, $F_{1,430}$ = 77.1; P = 0.000). Women treated with NTX stayed fewer days in treatment than men (χ^2_1 = 5.6; P = 0.03). The proportion of subjects who discontinued treatment was also significantly smaller in the EET group (35/162 vs. 190/273 CET; χ^2_1 = 17.8; P = 0.000). Approximately 58.4% of the dropouts (111/190) in the CET group and 34.3% (12/35) in the EET group occurred during the first week (χ^2_1 = 6.9; P = 0.01). Survival analyses confirmed that significantly more subjects dropped out in the CET group over the treatment period (χ^2 [Breslow] = 143.96; P = 0.000; Fig. 1).

The number of in-treatment negative UDS for opioids was higher among patients receiving NTX ($F_{1,398}$ = 59.6; P = 0.000), whereas no significant differences were found for other drugs of abuse. Thirty-two patients in the EET group used opioids during treatment and were restarted on NTX 1 mg. Patients who followed through with the referral to long-term programs for treatment continuation were 58% (93/162) in the EET group and 12.4% (34/273) in the CET group (χ^2_1 = 21.6; P = 0.000). The result of survival analyses was significant also in this case (χ^2 [Breslow] = 163.72; P = 0.000; Fig. 2). The proportion of subjects who completed treatment but did not meet the criteria of adherence with postdischarge care was comparable in the 2 groups (EET = 33/162; CET = 49/273; χ^2 = 0.26; P, not significant).

Treatment outcome results are summarized in Table 2.

To determine if the improved outcomes in EET were related to the influence of NTX on withdrawal symptoms, we compared daily withdrawal scores during the first week of treatment and found no significant difference between groups (repeated measure ANOVA, $F_{1,308}$ = 0.906; P = 0.770). Also, the peak withdrawal symptom score (the highest score achieved by each patient) was similar in the

TABLE 2. Treatment Outcome in Opioid-Dependent Subjects Accepting (EET) or Refusing (CET) Low-Dose NTX

Outcome Measures	EET (n = 162)	CET (n = 273)	F/χ^2
Days in treatment (1–21), mean (SD)	14.33 (6.51)	6.31 (6.3)	56.4*
Number of treatment sessions (0–6), mean (SD)	4.86 (1.82)	1.14 (1.1)	77.1*
Dropouts, %	21.6%	69.6%	66.4*
UDS-negative opioids (0–3), mean (SD)	1.26 (0.57)	0.39 (0.31)	56.8*
UDS-negative other drugs (0–3), mean (SD)	0.77 (0.79)	0.13 (0.76)	8.07
Continuation with treatment, %	58%	12.4%	99.5*

*P = 0.000.

2 groups (EET = 13.65, SD = 6.13, CET = 14.05, SD = 8.09; $F_{1,410}$ = 1,04; P = 0.406). Furthermore, the use of adjuvant drugs to control withdrawal symptoms was comparable in the 2 groups (data not shown). Because the presence of subjects with concomitant alcohol disorders could have affected the results of treatment in the EET group, we reanalyzed the data, restricting the EET sample to subjects without recently reported alcohol abuse (71/162), but differences in outcome between EET and CET groups remained essentially unchanged.

Low-Dose NTX Effect on Treatment Outcome

A linear regression analysis model was generated to evaluate the influence of NTX augmentation on primary outcome (days in treatment) and abstinence (number of negative UDS for opioids). The adjunct of low-dose NTX significantly affected retention in treatment ($F_{1,430}$ = 11.4; P = 0.002) and accounted for 11.5% of the variance in the outcome; on the other end, the influence of NTX on negative UDS was not significant ($F_{1,396}$ = 1.413; P = 0.162). When the effect of low-dose NTX on other measures of retention was investigated, the NNT for dropout and adherence with postdischarge care was 2 (95% confidence interval [CI], 2–3 in both cases; adjusted relative rate, 0.48; 95% CI, 0.39–0.57; and adjusted relative rate, 0.45; 95% CI, 0.37–0.52, respectively). Subject treated with NTX had a 69% reduction in risk of discontinuing treatment and a 78% increased possibility to follow through with aftercare, if compared with patients in the CET group.

Safety

In the EET group, 14 subjects (8.6%) experienced AEs, and 6 of them (5 were women) experienced a treatment-related AE. In the CET group, 20 patients (7.6%) experienced AEs, of whom, 11 (3 were women) experienced a treatment-related AE. Four subjects in this latter group discontinued treatment because of an AE. The most common treatment-related AEs were "dizziness" (67%), "fatigue" (55%), and "gastrointestinal upset" (39%). In 13 cases, patients reported redness of the skin surrounding the transdermal clonidine preparation, 4 of them were also receiving NTX. No treatment-related serious AEs were recorded.

DISCUSSION

The main findings of this study were the following: First, augmentation with low-dose NTX among preferred patients was superior to clonidine and psychosocial treatment alone. Second, the effectiveness of NTX augmentation was stronger on retention and aftercare compliance than on abstinence measures. Third, NTX treatment was characterized by a moderately low level of acceptance.

The administration of low-dose NTX as an adjunct to clonidine and psychosocial intervention after opioid detoxification was associated with better retention, reduced attrition, greater opioid abstinence and higher likelihood for subjects to continue on long-term outpatient treatment compared with clonidine and psychosocial treatment alone; on the other hand, the rather low rate of NTX acceptance was not influenced by a previous experience of the drug, confirming that antagonist treatment of opioid dependence is limited by negative attitudes.[10] The outcome was not affected by recent alcohol abuse, nor did it seem to be influenced by sex or ethnicity.

A large obstacle for outpatient drug-free programs is retaining patients in the first few weeks of treatment. Previous clinical investigations have reported that up to 50% of opiate addicts who were started on NTX after discharge from detoxification may drop out within days.[55,56] The attrition rate observed overall in our sample (51.7%) confirms that transition from an opioid agonist–assisted detoxification to drug-free condition is poorly tolerated. However, with low-dose NTX, the 3-week discontinuation rate was less than 22%, whereas retention (57.4%) fell in the range of results of clinical trials using methadone and other agonist drugs, including buprenorphine.[57–59] The most significant differences in dropout rates were associated with an NTX dosage range of 1 to 5 mg/d. This suggests that future dose-finding investigations should consider exploring the efficacy of dosages lower than 10 mg/d of NTX.

The effectiveness of low-dose NTX does not seem as a direct consequence of a reduction in withdrawal symptoms.[15] Possible explanations are that NTX is a deterrent of opioid use at low doses or that it modulates the effects of opioids at the mu receptor, preventing the development of adaptation, craving, and full relapse in the abuse.[24] An antipriming effect of low-dose NTX on opioid use may also resemble the mechanisms of NTX-induced reduction in alcohol pleasurable effects and consumption.[60] This hypothesis could also explain the stronger influence exerted by NTX on retention as opposed to opioid use, when considering the effects of treatment on outcomes. Interestingly, a reduction in craving and feelings of intoxication was observed in dose-response studies when comparable quantities of NTX were administered in the presence of opioids.[35] Such effects were not replicated with higher doses, and their clinical implications deserve further attention.

The outpatient administration of low doses of NTX after opioid detoxification was safe and well tolerated. Several patients used heroin and other drugs during treatment, as confirmed by UDS, but there was no evidence that such use was associated with significant withdrawal discomfort and AEs or led to treatment discontinuation.

The strengths of this investigation are to have studied a large sample size and a clinical population using a protocol that parallels a "real world", nonexperimental setting. Limitations include open-label design, nonrandom assignment, and lack of blindness. In addition, the brief duration of the treatment program where the pharmacological intervention was tested prevented us from drawing conclusions about long-term effectiveness. Another important limitation is that we did not provide a 'NTX plus psychosocial intervention' arm and therefore cannot exclude that the effectiveness of the treatment derived from the combination of NTX with clonidine.

We chose a self-selection, as opposed to a randomization design because we intended to reproduce the treatment options typically offered to opioid-dependent patients in clinical drug abuse programs. The study demonstrates the

effectiveness of the augmentation with low NTX among subjects who accept such treatment. It is worth noting that treatment self selection may not necessarily influence internal and external validity of the results in clinical pharmacological trials,[61] and this is confirmed in drug abuse studies.[62–64]

In conclusion, the indications of this study are the following: (1) adjunct low-dose NTX is safe, (2) it may be effective in the post-detoxification period of opioid dependence, and (3) it has moderately low acceptance. This pilot study suggests that adjunct low-dose NTX benefits opioid-dependent patients who accept the treatment. Given the open-label design, randomized, double-blind, placebo-controlled trials are necessary to fully evaluate the effectiveness of this treatment in opioid dependence.

ACKNOWLEDGMENTS

The authors thank the Coordinating Office for Drug and Alcohol Abuse Programs, Department of Public Health, Philadelphia, and Stephen P. Weinstein for recruitment; Edward Gottheil for treatment development and Charles C. Thornton for database preparation.

REFERENCES

1. O'Connor PG. Methods of detoxification and their role in treating patients with opioid dependence. *JAMA*. 2005;295:961–963.
2. Minozzi S, Amato L, Vecchi S, et al. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev*. 2006;1: CD00133.
3. O'Connor PG, Kosten TR. Rapid and ultrarapid opioid detoxification techniques. *JAMA*. 1998;279:229–234.
4. Gowing L, Ali R, White J. Opioid antagonists with minimal sedation for opioid withdrawal. *Cochrane Database Syst Rev*. 2002;1:CD002021.
5. Cornish JW, Metzger D, Woody GE, et al. Naltrexone pharmacotherapy for opioid dependent federal probationers. *J Subst Abuse Treat*. 1997;14: 529–534.
6. Roth A, Hogan L, Farren C. Naltrexone plus group therapy for the treatment of opiate-abusing health-care professionals. *J Subst Abuse Treat*. 1997;14:19–22.
7. Krupitsky EM, Zvartau EE, Masalov DV, et al. Naltrexone for heroin dependence treatment in St Petersburg, Russia. *J Subst Abuse Treat*. 2004;26:285–294.
8. Strang J, McCambridge J, Best D, et al. Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study. *BMJ*. 2003;326:959–960.
9. Digiusto E, Shakeshaft A, Ritter A, et al, The NEPOD Research Group. Serious adverse events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD). *Addiction*. 2005;99: 450–460.
10. Fram DH, Marmo J, Holden R. Naltrexone treatment—the problem of patient acceptance. *J Subst Abuse Treat*. 1989;6:119–122.
11. Forman RF, Bovasso G, Woody G. Staff beliefs about addiction treatment. *J Subst Abuse Treat*. 2001;21:1–9.
12. Mark TL, Dilonardo JD, Chalk M, et al. Factors associated with the receipt of treatment following detoxification. *J Subst Abuse Treat*. 2003;24:299–304.
13. Carrol KM, Ball SA, Nich D, et al. Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence efficacy of contingency management and significant other involvement. *Arch Gen Psychiatry*. 2001;58:755–761.
14. Rothenberg JL, Sullivan MA, Church SH, et al. Behavioral naltrexone therapy: an integrated treatment for opiate dependence. *J Subst Abuse Treat*. 2002;23:351–360.
15. Gowing L, Ali R, White J. Opioid antagonists and adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2000;2:CD002021.
16. Amato L, Davoli M, Minozzi S, et al. Methadone at tapered doses for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2005;20:CD003409.
17. Hollister LE, Johnson K, Boukhabza D, et al. Aversive effects of naltrexone in subjects not dependent on opiates. *Drug Alcohol Depend*. 1981;8:37–41.
18. Crowley TJ, Wagner JE, Zerbe G, et al. Naltrexone-induced dysphoria in former opioid addicts. *Am J Psychiatry*. 1985;142:1081–1084.
19. King AC, Volpicelli JR, Gunduz M, et al. Naltrexone biotransformation and incidence of subjective side effects: a preliminary study. *Alcohol Clin Exp Res*. 1997;21:906–909.
20. Oncken C, Van Kirk J, Kranzler HR. Adverse effects of oral naltrexone: analysis of data from two clinical trials. *Psychopharmacology*. 2001;154:397–402.
21. Lee MC, Wagner HN Jr, Tanada S, et al. Duration of occupancy of opiate receptors by naltrexone. *J Nucl Med*. 1988;29:1207–12011.
22. Bradley BP, Phillips G, Green L, et al. Circumstances surrounding the initial lapse to opiate use following detoxification. *Br J Psychiatry*. 1989;154:354–359.
23. De Vries TJ, Schoffelmeer AN, Binnekade R, et al. Drug-induced reinstatement of heroin- and cocaine-seeking behaviour following long-term extinction is associated with expression of behavioural sensitization. *Eur J Neurosci*. 1998;11:3565–3571.
24. Koob GF, Ahmed SH, Boutrel B, et al. Neurobiological mechanisms in the transition from drug use to drug dependence. *Neurosci Biobehav Rev*. 2004;8:739–749.
25. Shen KF, Crain SM. Ultra-low doses of naltrexone or etorphine increase morphine's antinociceptive potency and attenuate tolerance/dependence in mice. *Brain Res*. 1997;757:176–190.
26. Powell KJ, Abul-Husn NS, Jhamandas A, et al. Paradoxical effects of the opioid antagonist naltrexone on morphine analgesia, tolerance, and reward in rats. *J Pharmacol Exp Ther*. 2002;2:588–596.
27. Mannelli P, Gottheil E, Peoples JF, et al. Chronic very low dose naltrexone administration attenuates opioid withdrawal expression. *Biol Psychiatry*. 2004;56:261–268.
28. Lorenzi P, Marsili M, Boncinelli S, et al. Searching for a general anaesthesia protocol for rapid detoxification from opioids. *Eur J Anaesthesiol*. 1999;16:719–727.
29. Mannelli P, Gottheil E, Buonanno A, et al. Use of very-low dose naltrexone during opiate detoxification. *J Addict Dis*. 2003;22:63–70.
30. Chindalore VL, Cravven RA, Yu KP, et al. Adding ultralow-dose naltrexone to oxycodone enhances and prolongs analgesia: a randomized, controlled trial of Oxytrex. *J Pain*. 2005;6:392–399.
31. Judson BA, Carney TM, Goldstein A. Naltrexone treatment of heroin addiction: efficacy and safety in a double-blind dosage comparison. *Drug Alcohol Depend*. 1981;7:325–346.
32. Shufman EN, Porat S, Witztum E, et al. The efficacy of naltrexone in preventing reabuse of heroin after detoxification. *Biol Psychiatry*. 1994;35:935–945.
33. Rabinowitz J, Cohen H, Tarrasch R, et al. Compliance to naltrexone treatment after ultra-rapid opiate detoxification: an open label naturalistic study. *Drug Alcohol Depend*. 1997;25:77–86.
34. Rea F, Bell JR, Young MR, et al. A randomised, controlled trial of low dose naltrexone for the treatment of opioid dependence. *Drug Alcohol Depend*. 2004;75:79–88.
35. Comer SD, Collins ED, Kleber HD, et al. Depot naltrexone: long-lasting antagonism of the effects of heroin in humans. *Psychopharmacology*. 2002;159:351–360.
36. Foster J, Brewer C, Steele T. Naltrexone implants can completely prevent early (1-month) relapse after opiate detoxification: a pilot study of two cohorts totaling 101 patients with a note on naltrexone blood levels. *Addict Biol*. 2003;8:211–217.
37. Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Arch Gen Psychiatry*. 2006;63:210–218.
38. Dunbar JL, Turncliff RZ, Dong Q, et al. Single- and multiple-dose pharmacokinetics of long-acting injectable naltrexone. *Alcohol Clin Exp Res*. 2006;30:480–490.
39. Mattick RP, Kimber J, Breen C, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2003;2:CD002207.

40. Day E, Ison J, Strang J. Inpatient versus other settings for detoxification for opioid dependence. *Cochrane Database Syst Rev*. 2005;2:CD004580.
41. Fiorentine R, Anglin MD. Does increasing the opportunity for counseling increase the effectiveness of outpatient drug treatment? *Am J Drug Alcohol Abuse*. 1997;23:369–382.
42. O'Toole TP, Strain EC, Wand G, et al. Outpatient treatment entry and health care utilization after a combined medical/substance abuse intervention for hospitalized medical patients. *J Gen Intern Med*. 2002;17: 334–340.
43. Etheridge RM, Hubbard RL, Anderson J, et al. Treatment structure and program services in the Drug Abuse Treatment Outcome Study (DATOS). *Psychol Addict Behav*. 1997;11:244–260.
44. Fagan RW, Mauss AL. Padding the revolving door: an initial assessment of the Uniform Alcoholism and Intoxication Treatment Act in practice. *Soc Probl*. 1978;26:232–247.
45. Chutuape MA, Jasinski DR, Fingerhood MI, et al. One, three, and six-month outcomes after brief inpatient opioid detoxification. *Am J Drug Alcohol Abuse*. 2001;27:19–44.
46. Miller WR, Rollnick S. Motivational Interviewing: Preparing People to Change Addictive Behavior. New York: The Guilford Press; 1981.
47. Marlatt GA, Gordon JR. Relapse Prevention. New York: The Guilford Press; 1985.
48. Johnson PL. Evaluation of US Public Health Service programs. Organization and management. *Eval Health Prof*. 1996;19:311–324.
49. Derogatis LR, Yevzeroff H, Wittelsberger B. Social class, psychological disorder, and the nature of the psychopathologic indicator. *J Consult Clin Psychol*. 1975;43:183–191.
50. Beck AT. Beck Depression Inventory Manual. New York: Harcourt, Brace, Jovanovich, Inc; 1987.
51. Najavits LM, Gastfriend DR, Nakayama EY, et al. A measure of readiness for substance abuse treatment: psychometric properties of the RAATE-R interview. *Am J Addict*. 1997;6:74–82.
52. Handelsman L, Cochrane KJ, Aronson MJ, et al. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse*. 1987;13:293–308.
53. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ*. 1995;310:452–454.
54. Johansson BA, Berglund M, Lindgren A. Efficacy of maintenance treatment with naltrexone for opioid dependence: a meta-analytical review. *Addiction*. 2006;4:491–503.
55. Greenstein RA, O'Brien CP, McLellan AT, et al. Naltrexone: a short-term treatment for opiate dependence. *Am J Drug Alcohol Abuse*. 1981;8:291–300.
56. Tennant FS Jr, Rawson RA, Cohen AJ, et al. Clinical experience with naltrexone in suburban opioid addicts. *J Clin Psychiatry*. 1984;45: 42–45.
57. Ling W, Wesson DR, Charuvastra C, et al. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Arch Gen Psychiatry*. 1996;53:401–407.
58. Johnson RE, Chatuape MA, Strain EC, et al. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med*. 2000;343:1290–1297.
59. Stein MD, Cioe P, Friedmann PD. Buprenorphine retention in primary care. *J Gen Intern Med*. 2005;20:1038–1041.
60. O'Malley SS, Krishnan-Sarin S, Farren C, et al. Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo-pituitary-adrenocortical axis. *Psychopharmacology*. 2002;160:19–29.
61. King M, Nazareth I, Lampe F, et al. Impact of participant and physician intervention preferences on randomized trials: a systematic review. *JAMA*. 2005;293:1089–1099.
62. Gossop M, Johns A, Green L. Opiate withdrawal: inpatient versus outpatient programmes and preferred versus random assignment to treatment. *Br Med J*. 1986;293:103–104.
63. McKay JR, Rutherford MJ, Alterman AI, et al. An examination of the cocaine relapse process. *Drug Alcohol Depend*. 1995;38:35–43.
64. McKay JR, Alterman AI, McLellan AT, et al. Random versus nonrandom assignment in the evaluation of treatment for cocaine abusers. *J Consult Clin Psychol*. 1998;66:697–701.

