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The Combination Very Low-Dose Naltrexone–Clonidine in the Management of Opioid Withdrawal

Paolo Mannelli, M.D.[1], **Kathleen Peindl, Ph.D.**[1], **Li-Tzy Wu, Sc.D.**[1], **Ashwin A. Patkar, M.D.**[1], and **David A. Gorelick, M.D., Ph.D.**[2]

[1]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

[2]Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD, USA

Abstract

Background—The management of withdrawal absorbs substantial clinical efforts in opioid dependence (OD). The real challenge lies in improving current pharmacotherapies. Although widely used, clonidine causes problematic adverse effects and does not alleviate important symptoms of opioid withdrawal, alone or in combination with the opioid antagonist naltrexone. Very low-dose naltrexone (VLNTX) has been shown to attenuate withdrawal intensity and noradrenaline release following opioid agonist taper, suggesting a combination with clonidine may result in improved safety and efficacy.

Objectives—We investigated the effects of a VLNTX–clonidine combination in a secondary analysis of data from a double-blind, randomized opioid detoxification trial.

Methods—Withdrawal symptoms and treatment completion were compared following VLNTX (.125 or .25 mg/day) and clonidine (.1–.2 mg q6h) in 127 individuals with OD undergoing 6-day methadone inpatient taper at a community program.

Results—VLNTX was more effective than placebo or clonidine in reducing symptoms and signs of withdrawal. The use of VLNTX in combination with clonidine was associated with attenuated subjective withdrawal compared with each medication alone, favoring detoxification completion in comparison with clonidine or naltrexone placebo. VLNTX/clonidine was effective in reducing symptoms that are both undertreated and well controlled with clonidine treatment and was not associated with significant adverse events compared with other treatments.

Conclusions and Scientific Significance—Preliminary results elucidate neurobiological mechanisms of OD and support the utility of controlled studies on a novel VLNTX + low-dose clonidine combination for the management of opioid withdrawal.

Keywords

addiction; detoxification; antagonist; adrenergic; pharmacotherapies

Address correspondence to Paolo Mannelli, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, 2218 Elder Street, Suite 123, Durham, NC 27705, USA. Tel: 919-668-3757. Fax: 919-668-5418. paolo.mannelli@duke.edu.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

INTRODUCTION

Although continuous advances in the neurobiology of addiction may eventually lead to improved pharmacotherapies, the constant rise in health and social costs of opioid dependence (OD) (1) requires better ways of improving current treatments. Pharmacological approaches other than opioid agonist or antagonist maintenance consist of short-term withdrawal and medical stabilization to promote engagement in a continuum of care, and account for more than 40% of yearly opioid abuse treatment admissions in the United States (2). Short-term treatment modalities and outcomes can significantly affect delivery of and access to longer term interventions (3–5). For many years, the alpha-2 adrenergic agonist clonidine has been the mainstay of nonopioid treatment for relief of withdrawal symptoms during detoxification. By reducing noradrenergic activity and noradrenaline release, alpha-2-adrenergic agonist medications have shown to be as effective as methadone taper in managing withdrawal (6). However, clonidine does not consistently control a few important symptoms, such as anxiety, restlessness, and craving (7), or show reliable efficacy in combination with methadone taper (8,9). In addition, it is associated with problematic adverse effects, including hypotension and sedation that limit the use of higher doses or a treatment extension to the outpatient setting (10). Potential alternatives such as lofexidine are not approved for use in the United States and raise some concerns of cardiac adverse events when administered with methadone (11). Clonidine has been used in combination with naltrexone to reduce intensity and duration of withdrawal, but it is unclear whether this approach is more effective than managing withdrawal primarily with an adrenergic agonist (12). The rationale for adopting this combination is that clonidine may reduce withdrawal symptoms precipitated by naltrexone in patients with OD, whereas naltrexone would reset opioid receptor activity and compress withdrawal duration (13). A modality of naltrexone administration that does not increase withdrawal intensity, contributing instead to reduce its severity, may significantly improve the efficacy of this pharmacological combination.

Recently, we reported the results of a double-blind, placebo-controlled, randomized study showing that addition of very low-dose naltrexone (VLNTX) to methadone taper attenuates opioid withdrawal severity and craving during inpatient detoxification (14). A group of patients in this study also received clonidine treatment.

Here, we detail the results of a secondary analysis comparing the effects of VLNTX, clonidine, and their combination on opioid withdrawal severity and detoxification completion.

METHODS

Study Design

One hundred and seventy-four patients participated in a 6-day, double-blind, randomized trial, evaluating the safety and efficacy of two different oral naltrexone regimens (.125 and . 250 mg/day, respectively) for the treatment of opioid withdrawal during inpatient methadone-based detoxification at two community treatment programs. Clonidine (.1–.2 mg q6 h) was used at one study site. Only patients recruited at that site (N = 127) were included in the present evaluation.

Subjects and Procedures

The screening process, treatment, and evaluation procedures are described in detail elsewhere (14). Briefly, participants were 18 years or older nonmethadone-treated OD patients seeking detoxification. Potential subjects were excluded for any of the following criteria: hypersensitivity to NTX, pregnancy, psychiatric or medical conditions rendering

participation hazardous, and current dependence on alcohol and/or substances other than opioids or nicotine.

Psychiatric and medical examination with routine laboratory tests, including urine testing for drugs of abuse, were performed at screening. The Structured Clinical Interview for the Diagnostic and Statistical Manual 4th Edition (DSM-IV) (15) was used to formulate psychiatric diagnoses. The Addiction Severity Index (16) was used to evaluate drug use, social, and psychological status. Opiate withdrawal was evaluated using the Subjective Opiate Withdrawal Scale (SOWS) and the Objective Opiate Withdrawal Scale (OOWS) (17). One item of the SOWS was used to rate craving (18).

Treatments

Very Low-Dose Naltrexone—Participants were randomly assigned to one of the three inpatient conditions: (1) naltrexone placebo and methadone taper ($n = 54$); (2) naltrexone . 125 mg/day and methadone taper ($n = 35$); and (3) naltrexone .250 mg/day and methadone taper ($n = 38$).

Methadone—Subjects received methadone 30 mg on day 1, tapered by 5 mg/day, and were discharged on day 6. VLNTX was administered together with methadone.

Clonidine—Clonidine flexible dose (.1–.2 mg every 6 h) was routinely used for detoxification at the site chosen for this evaluation. However, a nonconsecutive group of patients ($n = 60$) did not receive the medication due to random, temporary unavailability.

Ancillary Medications—Ancillary medications were available as needed for all patients and included ibuprofen 200–400 mg and acetaminophen 325 mg orally (po) every 4–6 h for muscular/bone pain (q4-6h PRN); hydroxyzine 25–50 mg po q6h for nausea, vomiting, or anxiety; prochlorperazine 25 mg po q12h for nausea; loperamide 2–4 mg po q4–6h for diarrhea; and cyclobenzaprine 5 mg po q6h for myalgias or muscle spasm. Need for and use of ancillary medications were determined in routine clinical fashion by the nursing and medical staff.

In-Study Assessments

Daily evaluation was conducted prior to administration of methadone and naltrexone, using SOWS and OOWS scales. Adverse events were noted as reported by patients and observed during treatment.

Outcome Measures

The primary outcome measure was opioid withdrawal severity during the 6-day inpatient detoxification, assessed using SOWS and OOWS scales. Secondary measures were as follows: (1) retention in treatment based on the number of days from first dose to the last dose of study medication and measured by proportion of patients completing detoxification and (2) the use of ancillary medications, based on the number of subjects who received medications and quantity of medications administered.

Statistical Analysis

All analyses were carried out on the intent-to-treat sample. Demographic and clinical characteristics were compared using analysis of variance (ANOVA) for continuous variables and χ^2-test for categorical variables. Changes from baseline of SOWS and OOWS scores were analyzed using one-way repeated measures ANOVA with Bonferroni test to control for experimentwise errors. The same analyses were used for the comparison of daily dose of

medications and individual SOWS symptoms. A χ^2-test was used to compare groups on the percentage of participants retained through the entire detoxification, and time-to-event analysis using a log-rank test was used to compare groups on retention time.

RESULTS

Subjects

The 127 participants were divided into four treatment groups: VLNTX (NTX, $n = 39$), VLNTX plus clonidine (NTX/CLO, $n = 34$), clonidine (CLO, $n = 33$), and naltrexone placebo (NTX-PLA, $n = 21$) (Table 1). There was no significant difference in withdrawal intensity between patients randomized to different VLNTX doses, either administered alone (naltrexone .125 mg/day =17, .25 mg/day = 22) or with clonidine (naltrexone .125 mg/day = 18, .25 mg/day = 16) (data not shown). Patients receiving the two naltrexone doses were combined into one treatment condition in the NTX and NTX/CLO groups.

The characteristics of the sample are summarized in Table 1. There were no significant differences in demographic and clinical measures among the four groups or between patients who received clonidine and those who did not (data not shown). The daily dose of clonidine administered during the 6-day detoxification treatment did not significantly differ between NTX/CLO and CLO groups ($F = 1.2(1,76)$, $p = .9$).

Opioid Withdrawal

Patients treated with VLNTX reported significantly lower SOWS scores compared with clonidine or naltrexone placebo (Figure 1, SOWS, $F = 7.8(3127)$, $p = .003$; for NTX vs. NTX-PLA, $p = .001$; for NTX vs. CLO, $p = .01$). Individuals in the NTX/CLO group reported attenuated withdrawal compared with those in the NTX ($p = .03$) or CLO ($p = .01$) groups. No significant differences were found in subjective withdrawal scores between patients receiving clonidine or naltrexone placebo (CLO vs. NTX-PLA $p = .18$).

Objective withdrawal scores were significantly lower among patients treated with VLNTX compared with clonidine or naltrexone placebo (OOWS, $F = 4.9(3125)$, $p = .02$; for NTX vs. NTX-PLA, $p = .03$; for NTX vs. CLO, $p = .03$). No significant differences in objective withdrawal intensity were noted between NTX and NTX/CLO groups ($p = .07$) or between CLO and NTX-PLA groups ($p = .23$).

Withdrawal Symptoms

To characterize the effects of different treatments, individual SOWS symptoms were compared between the CLO group and the NTX/CLO and NTX groups. NTX/CLO patients showed significantly reduced intensity of shaking, anxiety, bone and muscle aches, restlessness, and craving, as well as lacrimation, rhinorrhea, and sweating compared with the CLO ones (F range = 4.9–10.1(1,67), $p = .03$–.001). The NTX group showed a more significant reduction in muscle twitching, restlessness, anxiety, and craving than the CLO group (F range = 4.1–9.2(1,72), $p = .02$–.001).

Treatment Retention

Eighty-five patients (66.9%) completed treatment. There were significant differences in study retention among the four groups (NTX, 64.1%; NTX/CLO, 85.3%; CLO, 60.6%; and NTX-PLA, 52.4%; $\chi^2 = 7.9$, df = 3, $p = .043$). Pairwise comparisons showed significantly greater retention among patients receiving VLNTX + clonidine than among those taking clonidine or ancillary medications alone (NTX/CLO vs. CLO, $p = .01$; NTX/CLO vs. NTX-PLA, $p = .002$).

Use of Ancillary Medications and Adverse Events

All subjects received ancillary medications following an established clinical routine. The mean (SD) dose of medication received per subject per day was 647.2 mg (180.2) ibuprofen, 707.0 mg (172.1) acetaminophen, 6.8 mg (1.3) loperamide, 43.9 mg (4.0) hydroxyzine, 7.6 mg (1.2) prochlorperazine, and 8.2 mg (2.6) cyclobenzaprine. There were no significant differences in amount of each ancillary medication administered to the four treatment groups during the 6-day detoxification treatment (F range = .47–1.82(3); p = .10–.75).

There were no serious adverse events and no medication-related adverse events. None of the adverse events recorded and previously described in this sample (14) occurred in clonidine-treated patients. The only other adverse events were mild somatic and behavioral complaints indistinguishable from signs of opiate withdrawal that were documented by withdrawal scores. There were no episodes of medication-precipitated withdrawal. There were no significant group differences in peak Heart Rate (HR) (F = .64(3); p = .81; total mean (SD) = 71.9 (9.6)) or peak systolic (F = 1.07(3); p = .19; total mean (SD) = 102.8 (19.8)) or diastolic Blood Pressure (BP) (F = .44(3); p = 1.17; total mean (SD) = 59.6 (9.9)).

DISCUSSION

This secondary analysis of previously presented data shows that VLNTX was more effective than clonidine or naltrexone placebo in easing symptoms and signs of withdrawal during methadone taper. The combination of VLNTX with clonidine attenuated subjective withdrawal more than each medication alone and resulted in higher rate of detoxification completion compared with clonidine or naltrexone placebo treatments.

Potential modifiers of treatment effects, such as sociodemographic and drug use characteristics, or PRN use of ancillary medications during detoxification did not differ significantly between groups. It is unlikely that such variables influenced the findings.

The efficacy of VLNTX treatment confirms results observed in the primary study (14). The lack of significant symptom improvement following clonidine treatment was associated with lack of adverse effects such as hypotension and may be due to the rather low doses of medication used (see Table 1). Previous studies indicate that comparable doses have limited efficacy in controlling withdrawal (19), while higher, more effective dosing regimens are associated with side effects that can significantly limit its use (12,20).

The VLNTX + clonidine combination was safe and attenuated opioid withdrawal symptoms commonly undertreated during clonidine-based methadone detoxification, such as anxiety, restlessness, and craving (7,20). The combination treatment was also more effective in reducing the intensity of symptoms usually well controlled with alpha-2 adrenergic agonism, such as lacrimation, rhinorrhea, and sweating (20,21). The efficacy of VLNTX–clonidine seems to be in line with preclinical evidence on functional interactions of opioid and adrenergic pathways (22). Mu and alpha-2-adrenergic receptors influence each other's action (23,24). In particular, VLNTX downregulates mu receptor activity in brain noradrenergic areas during chronic opioid exposure, reducing noradrenaline release upon withdrawal (25,26). If VLNTX and clonidine display additive or synergistic action, withdrawal control would be achieved using a lower clonidine dose, thus reducing the incidence of adverse events. Interestingly, clonidine shows conditioned aversion and reinforcing or discriminative stimulus properties that are detectable at low or very low doses in animals (27–29).

This study has several limitations. Patients were randomized to receive VLNTX or placebo, not clonidine. The daily doses of clonidine and ancillary medications were decided by

medical staff and not by investigators at the study site. Confounding by individual differences in treatment-relevant variables is unlikely because participants did not significantly differ in such characteristics, while the potential influence of external variables was mitigated by limiting the study sample to the site where clonidine was routinely used. However, it is possible that the effects of the combination VLNTX–clonidine on opioid withdrawal are accounted for by unmeasured confounds, and the results should be considered preliminary.

Although opioid detoxification *per se* should not be considered as a treatment for OD, much of the clinical effort is spent to offer a more comfortable reduction or discontinuation of opioid agonist medications. Despite the limitations, this study provides indication that using VLNTX + low-dose clonidine is safe and more efficacious than using each single treatment to reduce withdrawal intensity during opioid agonist taper. The investigation of its effects can contribute to shed light on the mechanisms of regulation of OD and withdrawal. Controlled studies should evaluate the effectiveness of this drug combination in different conditions of detoxification and transition from opioid agonist to antagonist treatment, including the use of partial agonist and the outpatient setting.

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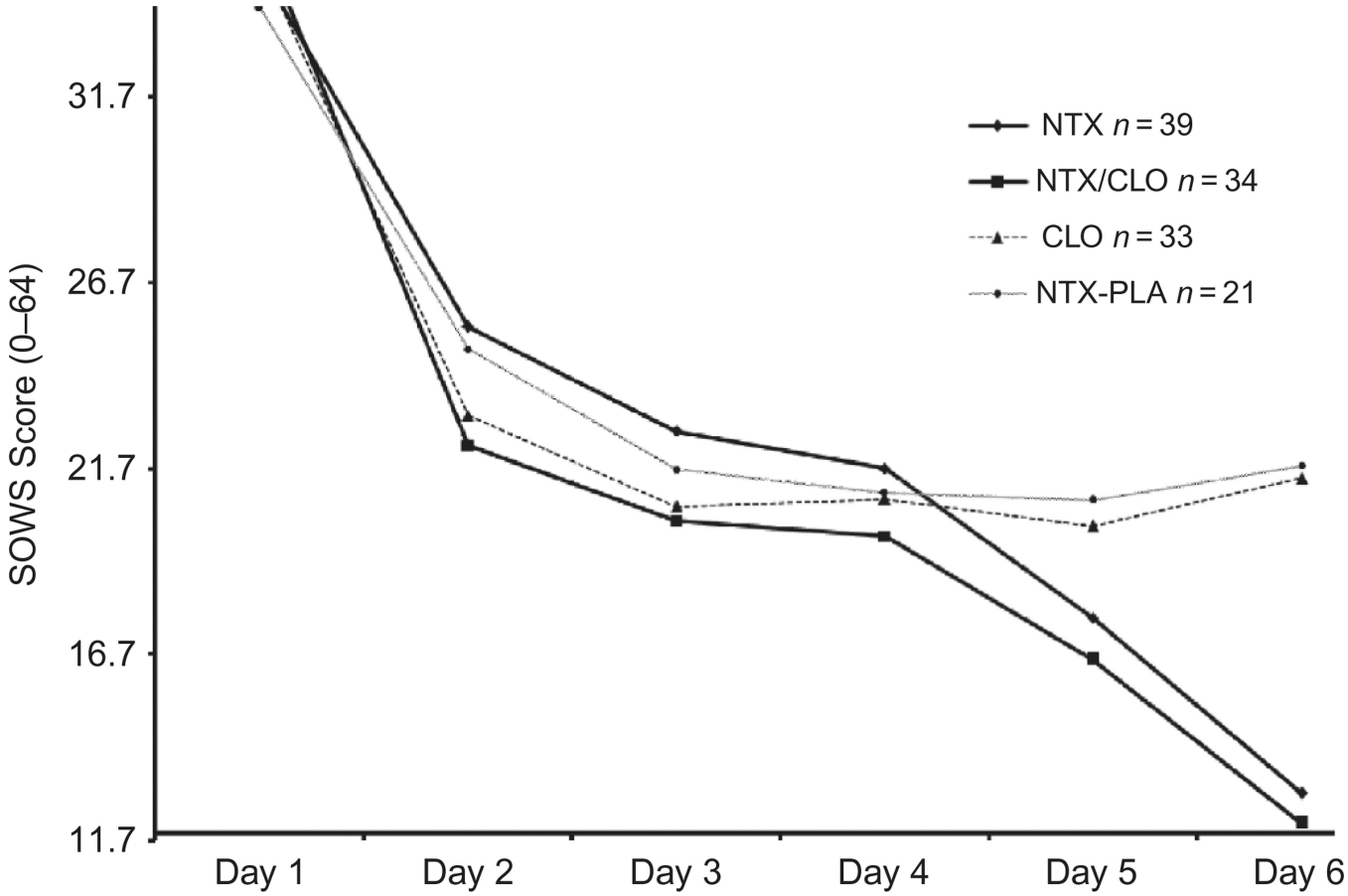

FIGURE 1.

Subjective Opiate Withdrawal Scale scores of 127 opioid-dependent inpatients undergoing 6-day methadone detoxification. NTX = very low naltrexone patients, NTX/CLO = very low naltrexone plus clonidine patients, CLO = clonidine patients, and NTX-PLA = naltrexone placebo patients. Very low naltrexone use was associated with significantly attenuated withdrawal (repeated measures analysis of variance (ANOVA), change of scores, $F = 7.8(3127)$, $p = .003$; for NTX vs. AM, $p = .001$; for NTX vs. CLO, $p = .02$). Patients receiving NTX + CLO reported less intense withdrawal compared with those from the NTX ($p = .03$) or CLO ($p = .01$) groups.

TABLE 1

Sociodemographic, substance use characteristics, and detoxification treatment status of 127 opioid-dependent inpatients undergoing 6-day methadone detoxification.

	NTX (*n* = 39)	NTX/CLO (*n* = 34)	CLO (*n* = 33)	NTX-PLA (*n* = 21)
Percentage or mean (SD)				
Demographics				
Age	32.2 (6.2)	33.8 (5.6)	31.9 (6.1)	30.18 (9.1)
Male	69.2	67.6	63.6	61.9
African-American	28.2	32.3	20.6	19.8
Years of education	10.3 (4.2)	9.8 (2.2)	7.8 (1.7)	11.1 (2.9)
Married or cohabitant	23	16.2	15.2	19
Unemployed	59	61.7	60.6	66.7
Substance use				
Days of use in last month				
Opioids	20.6 (4.9)	17.9 (2.5)	22 (4.5)	20.7 (3.4)
Alcohol	6.8 (4.5)	9.9 (6.9)	3.6 (5.1)	5.7 (6.6)
Cannabis	5.5 (5.2)	8.9 (4.5)	8.2 (9.5)	7.5 (2.9)
Cocaine	9.7 (6.6)	12.1 (8.9)	10.6 (4.1)	8.9 (2.1)
Years of use				
Opioids	8.3 (6.7)	7.7 (5.7)	7.7 (1.9)	8.7 (6.3)
Alcohol	8.9 (6.8)	7.6 (7.1)	4.9 (4.8)	5.9 (3.1)
Cannabis	5.6 (4.2)	6.6 (3.5)	7.6 (3.1)	7.6 (3.1)
Cocaine	7.8 (2.8)	6.7 (5.2)	5.2 (4.2)	6.9 (6.4)
Addiction Severity Index				
Drug Composite Score	.27 (.11)	.28 (.17)	.21 (.17)	.30 (.11)
Alcohol Composite Score	.09 (.29)	.11 (.26)	.03 (.28)	.05 (.18)
Psychiatric Composite Score	.26 (.23)	.27 (.21)	.26 (.13)	.22 (.21)
Other drug tests at admission				
Positive cocaine	48.7	52.9	57.5	52.4
Positive cannabis	43.6	41.2	51.5	42.8
Positive amphetamine	5.1	5.8	6.1	4.8
Treatments				
Naltrexone placebo	–	–	100	100
Naltrexone (.125 mg/day)	43.6	52.9	–	–
Naltrexone (.250 mg/day)	65.4	47.1	–	–
Clonidine (mg/day)	–	.43 (.11)	.49 (.19)	–
Ancillary medications (y/n)	y	y	y	y

Notes: All comparisons were nonsignificant ($p > .05$). NTX = very low naltrexone, NTX/CLO = very low naltrexone plus clonidine, CLO = clonidine, NTX-PLA = naltrexone placebo, and y/n = yes/no.