Long-Acting Injectable Versus Oral Naltrexone Maintenance Therapy With Psychosocial Intervention for Heroin Dependence: A Quasi-Experiment

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Objective: To conduct a quasi-experimental comparison of early clinical outcomes between injectable, sustained-release, depot naltrexone formulation versus oral naltrexone maintenance therapy in individuals with opiate dependence.

Method: Early retention in treatment and urine-confirmed opiate use in the first 8 weeks postdetoxification were compared between patients (diagnosed as opiate-dependent according to *DSM-IV* criteria) participating in 2 concurrently run randomized clinical trials of oral (n = 69; patients treated from September 1999 to May 2002) and long-acting injectable (n = 42; patients treated from November 2000 to June 2003) naltrexone maintenance therapy with psychosocial therapy.

Results: Long-acting injectable naltrexone produced significantly better outcome than oral naltrexone on days retained in treatment ($F_{1,106} = 6.49$, $P = .012$) and for 1 measure of opiate use ($F_{1,106} = 5.26$, $P = .024$); other measures were not significantly different, but differences were in the same direction. In subanalyses, there were interaction effects between baseline heroin use severity and type of treatment. In subanalyses, heroin users with more severe baseline use showed better retention with oral naltrexone maintenance therapy combined with intensive psychotherapy (behavioral naltrexone therapy) as compared to retention shown by severe heroin users treated with long-acting naltrexone injections combined with standard cognitive-behavioral therapy ($\chi^2_1 = 9.31$, $P = .002$); less severe heroin users evidenced better outcomes when treated with long-acting injectable naltrexone.

Conclusions: This quasi-experimental analysis provides tentative indications of superior outcomes for heroin-dependent patients treated with long-acting injectable naltrexone compared to oral naltrexone. The finding that heroin users with more severe baseline use achieved better outcomes with oral naltrexone is most probably attributable to the intensive nature of the psychosocial treatments provided and points to the opportunity for continued research in augmenting injectable naltrexone with psychosocial strategies to further improve outcome, especially in individuals with more severe use. The results should be considered exploratory given the quasi-experimental nature of the study.

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The high-affinity opioid receptor antagonist naltrexone is a theoretically powerful treatment for opioid dependence, but it has had only very limited effectiveness because of poor adherence to treatment with the medication in pill form.[1] It is simply too easy for patients to stop the pills for a few days, after which the blockade wears off and relapse to opioid dependence usually ensues.[2] Numerous behavioral strategies have been attempted to increase outpatient compliance with oral naltrexone among opioid-dependent patients, including contingency management with money and vouchers, behavior therapy, and the inclusion of significant others in conjoint sessions or as medication monitors,[3–10] although meta-analytic reviews of such studies demonstrate that such strategies have at best a moderate impact on outcome.[6,10] Newly developed long-acting injectable and implantable naltrexone formulations have the potential to reduce the adherence problem and substantially improve the effectiveness of naltrexone as a treatment alternative for opioid dependence.[11,12] However, there are no published randomized controlled trials comparing outcomes for long-acting injectable naltrexone versus oral naltrexone for opioid dependence. Three quasi-experimental reports[13–15] that compare oral naltrexone outcomes to outcomes from naltrexone implants from treatment providers who offered both forms of treatment plus counseling demonstrate that patients receiving implant treatment demonstrated significantly better opiate abstinence and treatment retention at 6-month and 12-month follow-up points. A randomized controlled trial comparing injectable naltrexone to oral naltrexone is underway in Russia, and interim results show significantly improved outcomes for patients assigned to injectable naltrexone.[16]

At the Substance Treatment and Research Service (STARS) at the New York State Psychiatric Institute, New York, New York, we conducted concurrent randomized clinical trials investigating long-acting injectable naltrexone, in collaboration with investigators from the University of Pennsylvania, Philadelphia,[11] as well as behavioral interventions to improve oral naltrexone compliance.[6] These recent trials provide an excellent opportunity to examine differences in early retention and urine-confirmed heroin use outcomes between similar groups of heroin-dependent individuals. Despite the given limitations of a quasi-experimental study (nonrandomization to groups and potential selection biases), a strong case can be made for this comparison because patients in both trials were recruited concurrently and were treated at the same clinic by overlapping staff, with many

similarities in background treatment. All participants in both trials completed inpatient, buprenorphene-naltrexone–assisted detoxifications and then received either long-acting injectable or oral formulation of active naltrexone in separate randomized clinical trials.

In the present analysis, we compared retention and opiate-use differences in the first 8 weeks of treatment postdetoxification between patients receiving long-acting injectable formulation and patients receiving oral formulation. These 2 trials were of varying length; the oral naltrexone study[6] lasted for 24 weeks, while the injectable naltrexone study[11] lasted only 8 weeks. Comparisons to the 8-week injectable naltrexone study[11] were drawn from the first 8 weeks of the oral naltrexone study.[6] This analysis examined primarily length of time retained in treatment and opiate use while in treatment; the variables chosen for analysis (time retained, rate of dropout, and proportion of opiate-negative urine samples) were selected because they were primary outcomes used in both of the previous published reports.[6,11] We controlled for group differences on baseline patient characteristics. Given the small sample size, we included only 1 potentially moderating variable; our previous work has shown that baseline severity of opiate use can interact with treatment condition, with patients who have higher severity of use benefiting from more intensive psychosocial treatment.[2] We included this severity variable as a potential moderator in all analyses.

In this comparison study, approximately half of the patients receiving injectable naltrexone received a less-than-therapeutic dose of naltrexone (192 mg), as determined by a previous laboratory study showing that antagonism effects began to diminish by week 4.[17] In addition, half of the patients receiving oral naltrexone received a much less active psychosocial treatment (compliance enhancement). To estimate the effectiveness of depot naltrexone and oral naltrexone under more optimal conditions as it might be delivered in actual clinical practice (ie, full dose of injectable naltrexone with integrated, evidence-based psychosocial treatment), we conducted a series of subanalyses comparing outcomes between behavioral naltrexone therapy (BNT) (an intensive psychosocial treatment combined with oral naltrexone) and full-dose, long-acting injectable naltrexone combined with only moderate psychosocial intervention. These exploratory subanalyses were conducted to assess the degree to which intensive psychosocial strategies may provide comparable results to long-acting injectable naltrexone treatment.

METHOD

Participants

Recruitment, screening, and eligibility criteria have been described extensively in earlier published reports[6,11] and are summarized here. Candidates were treatment-seeking heroin users recruited to a research clinic at an urban academic medical center, primarily through newspaper advertisements designating no-cost, confidential treatment for heroin problems in a research setting. Eligibility criteria across the 2 research protocols varied slightly but shared in common the following requirements: patients had to be aged 18 to 59 and they had to meet *DSM-IV* criteria for opiate dependence without unstable medical disorders. In both research protocols, participants were excluded if they exhibited any major Axis I disorders such as schizophrenia or bipolar disorder. Both studies permitted participants who exhibited symptoms of depression and anxiety, which are fairly common in opiate dependence but often remit with naltrexone treatment (eg, diagnoses of substance-induced mood disorder, major depressive disorder, and anxiety disorder not otherwise specified were acceptable). Participants in both studies were assessed using the Hamilton Depression Rating Scale (HDRS)[18] to establish baseline level of psychiatric functioning. In the injectable naltrexone study,[11] participants could not be dependent on any substances other than opiates, nicotine, and caffeine. Concurrent dependencies on other substances were acceptable in the oral naltrexone study[6] as long as opiate dependence was determined to be primary; in addition, candidates in the oral naltrexone study[6] had to have a non–substance-abusing significant other, relative, or sponsor who was prescreened and willing to participate in treatment. Both research protocols were approved by the New York State Psychiatric Institute Institutional Review Board, and all participants provided informed consent.

Measures

This quasi-experimental analysis includes retention and substance use outcome measures analyzed in the original reports.[6,11]

Retention. Retention is measured in number of days retained across the first 8 weeks of treatment postdetoxification and is measured categorically in terms of whether a patient is retained by 8 weeks. Patients were considered dropped from treatment after 2 weeks absence from the clinic.

Urinalysis. An observed urine sample was collected at all outpatient visits. This analysis employed a comparison of proportions of opiate-negative urine samples across treatment, with missing samples analyzed in 2 ways: dropped from analysis and imputed as positive.

Procedures

Patients treated in the conditions in the following comparison received similar clinical care; differences between protocols are summarized here. Detailed descriptions of protocols can be found in the published reports.[6,11]

Across conditions, all patients completed an 8-day buprenorphine-assisted detoxification and transition to naltrexone procedure on a locked inpatient research ward. During the outpatient phase of treatment, patients attended twice-weekly psychosocial treatment. At these visits, patients provided urine samples, were evaluated by the clinic nursing staff, and saw a clinician for the specified psychosocial treatment. The clinicians (doctoral- and predoctoral-level psychologists) providing the psychosocial treatment were trained in the manualized approaches, and sessions were audiotaped for supervision purposes. Patients were paid nominally for compliance with research visits at various

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data collection intervals and were also provided a transportation stipend covering the cost of public transportation to the clinic.

The treatment groups differed in procedures in the following ways:

Oral naltrexone maintenance therapy.[6] Detoxified patients were provided with oral naltrexone (50 mg/d) and were randomly assigned to behavioral naltrexone therapy (oral/BNT) or compliance enhancement therapy (oral/CE). Oral/BNT[8] strategically integrates several evidence-based behavioral approaches, including elements of cognitive-behavioral relapse prevention therapy,[19,20] network therapy,[21] and voucher incentives (to a maximum of $28 per week, or $224 for the 8-week portion of the study under consideration) for patients with opiate-negative urine samples.[22] Weekly sessions with the patient's significant other focused on monitoring naltrexone ingestion and engaging the significant other in supporting relapse prevention. Oral/CE is a manual-guided intervention[23] delivered by experienced psychiatrists designed as a control condition for medication trials and intended to simulate standard clinic or office-based care, encourage medication compliance, and control for professional attention. Patients were treated in this study from September 1999 to May 2002.

Long-acting injectable naltrexone therapy.[11] Detoxified patients were randomly assigned to receive 1 of 3 levels of an injectable, sustained-release, depot formulation of naltrexone: (1) placebo and cognitive-behavioral therapy (CBT), (2) low-dose naltrexone (192 mg) and CBT, or (3) high-dose naltrexone (384 mg) and CBT. Four weeks later, patients received a second identical dose of the study medication. Patients received twice-weekly, manualized cognitive-behavioral relapse prevention therapy.[18] Patients were treated in this study from November 2000 to June 2003. Twenty-one percent of this treatment group (9 of 42 patients) were recruited, enrolled, and treated at the University of Pennsylvania Treatment Research Center, Philadelphia, Pennsylvania.

Analysis

Differences between groups on demographic and heroin use variables were examined and described, employing χ^2 and *t* tests to test between groups on categorical and continuous variables. Detected differences between comparison groups were controlled for in outcome analyses. After determining which patient-level variables needed to be controlled in each set of analyses, we ran the analyses both with and without the covariates. In all cases, the results, including mean square, *F* values, and *P* values, of the treatment effects were similar.

The analysis was conducted in 2 stages. First, patients (N = 111) were collapsed across type of naltrexone they received to compare long-acting injectable naltrexone (n = 42; patients receiving placebo were excluded) with oral naltrexone (n = 69). Second, a set of analyses on a smaller sample (n = 58) was conducted to estimate the effectiveness of full-strength injectable naltrexone (384 mg) compared to oral naltrexone combined with intensive therapy; we included this set of subanalyses to more closely approximate effectiveness under typical clinical conditions (ie, full dose of injectable naltrexone, active evidence-based psychosocial treatment). Patients receiving full-strength long-acting injectable naltrexone (384 mg) and cognitive-behavioral therapy (high dose/CBT) were compared to patients receiving oral naltrexone and intensive psychosocial treatment (oral/BNT). Mean number of days retained was analyzed with analysis of covariance (ANCOVA), and time to dropout was analyzed with Cox regression survival analysis. Opiate use was compared by employing ANCOVA to examine differences across groups in proportion of opiate-negative urine samples; a second set of analyses was included with missing urine samples imputed as positive. Both sets of analyses also included the interaction term between baseline opiate use severity (number of bags of heroin used per day) and the treatment group, as this interaction has been previously demonstrated to moderate the effects of psychosocial treatment when compared to a control condition of oral maintenance therapy.[2]

Number of days retained was moderately negatively skewed, although within the acceptable range, and proportion of opiate-negative urine samples was more severely positively skewed. We ran a similar set of analyses using nonparametric tests (ie, Mann-Whitney, Kolmogorov-Smirnov) to verify that high skewness values were not inflating our results. In all cases, the results were quite similar, assuring us that issues of skewness were not hampering our analyses.

RESULTS

Patient Characteristics

Combining the patients from each experimental group yielded 111 heroin-dependent patients who completed detoxification and were discharged into outpatient naltrexone maintenance therapy. Descriptive statistics broken down by group are presented in Table 1. The majority of patients (80.2%) were male, were not currently in a cohabiting or marital relationship (75.7%), and were a mean age of 37.6 years (SD = 10.0 years). The majority of patients (46.8%) were white, with 24.3% identifying as African American, 26.1% identifying as Hispanic, and 2.7% identifying as another race.

Patients reported using a mean of 6.1 bags of heroin per day (SD = 3.7 bags/day), and half (52.4%, n = 77) reported using heroin intranasally. Intravenous injection was reported as the main route of heroin use by 37.4% of patients. The remainder of patients either smoked (5.4%) or injected heroin subcutaneously (1.4%), with 3.4% unknown. Patients reported using heroin regularly for a mean of 10.2 years (SD = 9.7 years). Mean baseline 21-item HDRS scores were 12.54 (SD = 6.50) and did not differ significantly between groups.

As specified in the exclusion criteria, patients in the long-acting injectable study[11] could not meet criteria for dependence on any illicit substances other than opiates. Patients in the oral naltrexone study could meet criteria for dependence on other substances. However, rates of other substance dependencies in the oral naltrexone study were

Table 1. Descriptive Characteristics, Retention Rates, and Substance Use Outcomes Across High-Dose and Low-Dose Injection Groups From the Comer et al[11] Study of Long-Acting Injectable Naltrexone and Across Behavioral Naltrexone Therapy (BNT) and Compliance Enhancement Therapy (CE) Conditions of Oral Naltrexone Maintenance From the Nunes et al[6] Study

	Long-Acting Injectable Naltrexone		Combined	Oral Naltrexone		Combined
Variable	High Dose/CBT (n = 22)	Low Dose/CBT (n = 20)	Injection Group (N = 42)	Oral/BNT (n = 36)	Oral/CE (n = 33)	Oral Group (N = 69)
Gender, male, % (n)	86.4 (19)	75.0 (15)	81.0 (34)	77.8 (28)	81.8 (27)	79.7 (55)
Race, % (n)						
White	36.4 (8)	35.0 (7)	35.7 (15)	50.0 (18)	57.6 (19)	53.6 (37)
African American	40.9 (9)	35.0 (7)	38.1 (16)	19.4 (7)	12.1 (4)	15.9 (11)
Hispanic	13.6 (3)	25.0 (5)	19.0 (8)	30.6 (11)	30.3 (10)	30.4 (21)
Other	9.1 (2)	5.0 (1)	7.1 (3)	0 (0)	0 (0)	0 (0)
Age, mean (SD), y	40.6 (10.5)	42.1 (10.5)	41.3 (10.4)	36.3 (10.2)	34.3 (7.7)	35.3 (9.1)
In cohabiting relationship, % (n)						
Yes	27.3 (6)	40.0 (8)	33.3 (14)	19.4 (7)	18.2 (6)	18.8 (13)
No	72.7 (16)	60.0 (12)	66.7 (28)	80.6 (29)	81.8 (27)	81.2 (56)
21-item Hamilton Depression Rating Scale score, mean (SD)	11.8 (6.4)	11.8 (5.5)	11.8 (5.9)	13.4 (6.8)	12.5 (7.0)	13.0 (6.9)
Years of heroin use, mean (SD)	12.2 (12.3)	13.6 (12.2)	12.9 (11.2)	11.0 (9.4)	6.3 (5.0)	8.7 (7.9)
Bags of heroin used per day, mean (SD)	6.4 (4.0)	5.4 (4.2)	5.9 (4.1)	6.5 (3.4)	6.1 (3.7)	6.3 (3.6)
Route of heroin use, % (n)						
Intranasal	36.4 (8)	60.0 (12)	47.6 (20)	61.1 (22)	60.6 (20)	60.9 (42)
Intravenous	45.5 (10)	20.0 (4)	33.3 (14)	36.1 (13)	39.4 (13)	37.7 (26)
Subcutaneous	NA	5.0 (1)	2.4 (1)	NA	NA	NA
Smoked	4.5 (1)	5.0 (1)	4.8 (2)	2.8 (1)	NA	1.4 (1)
Patients completing 8 treatment weeks, % (n)	68.2 (15)	45.0 (9)[a]	57.1 (24)	47.2 (17)	30.3 (10)	39.1 (27)
Days retained, mean (SD)	47.7 (15.8)	36.5 (19.3)	42.3 (18.2)	36.6 (21.4)	26.8 (22.7)	31.9 (22.4)
Percentage of missing urine samples per condition	34.1	46.8	40.2	47.7	63.6	55.3
Patients testing positive for opiates, % (N)	50.0 (11)	50.0 (10)	50.0 (21)	58.3 (21)	51.5 (17)	55.1 (38)
Proportion of opiate-negative urine samples, mean (SD)	0.78 (0.33)	0.74 (0.35)	0.76 (0.34)	0.66 (0.37)	0.75 (0.33)	0.70 (0.35)
Proportion of opiate-negative urine samples (missing samples imputed as positive), mean (SD)	0.57 (0.31)	0.46 (0.37)	0.52 (0.34)	0.40 (0.35)	0.34 (0.30)	0.37 (0.33)

[a]Percent of patients retained in the low-dose injection/CBT group differs from that previously reported by Comer et al[11] for the 192-mg dose, as the current report adopted a more rigorous threshold for classifying patients as dropped from treatment. Three patients who were considered completers in the Comer et al[11] study were reclassified as dropouts due to a > 2-week absence from the clinic during treatment.
Abbreviations: CBT = cognitive-behavioral therapy, NA = not applicable.

quite low: cocaine (7%), marijuana (3%), alcohol (7%), and sedatives (1%).

The majority of patients in the long-acting injectable study were treated at STARS (Substance Treatment and Research Service) in New York City, which was also the site of the oral naltrexone study; 4 patients from the low-dose injection/CBT group and 5 patients from the high-dose injection/CBT group were treated at the University of Pennsylvania in Philadelphia. These patients did not differ from the STARS patients in the injectable naltrexone treatment groups on any retention or opiate use variable and did not differ significantly from the STARS patients on any demographic variable except for age; patients treated at the University of Pennsylvania were a mean of 10 years older than patients treated at STARS ($t_{40} = 2.79$, $P = .008$). However, since age was not correlated with any outcome variable in these groups, this difference was ignored, and the University of Pennsylvania patients were included in the analysis. Percentages of patients completing 8 weeks of treatment, mean days retained in treatment, and mean proportion of heroin-negative urine samples across the 4 treatment groups are also presented in Table 1.

Collapsed Conditions: Long-Acting Injectable Versus Oral Naltrexone Treatment

High-dose and low-dose injection conditions and BNT and CE conditions were combined. There were significant demographic differences found between the injection and oral treatment groups. Patients receiving long-acting injections tended to be older (injection: mean = 41.3 years; oral: mean = 35.3 years; $t_{109} = 3.18$, $P = .002$), had a longer history of regular heroin use (injection: mean = 12.9 years; oral: mean = 8.7 years; $t_{109} = 2.30$, $P = .024$), and were more likely to be African American than were patients receiving oral naltrexone (38% in the injection group, 16% in the oral group; $\chi^2_3 = 13.28$, $P = .004$). All analyses exploring differences between oral and injection conditions controlled for these 3 variables.

Fifty-seven percent of injection group patients and 42% of oral group patients completed 8 weeks of treatment. Sixty-seven percent (28 of 42) injection group patients consented to receive the second dose of injectable naltrexone after 4 weeks; patients not receiving the second dose often dropped from treatment at or just before the 4-week point. Injection group patients remained in treatment for a mean of 42.3 days (SD = 18.2 days), while oral group patients remained in treatment for a mean of 31.9 days (SD = 22.42 days). When we controlled for differences between groups, this difference was statistically significant ($F_{1,106} = 6.49$, $P = .012$); Table 2 shows the full model. Cox survival analysis showed no difference between conditions on rate of dropout (Exp[B] = 0.75, $P = .20$). The interaction between treatment condition and severity of baseline heroin use was included in these 2 analyses but was not found to be significant and so was dropped from the models.

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Table 2. Adjusted Means, Standard Deviations, and Analysis of Covariance Models[a] Comparing Oral Naltrexone Versus Depot Naltrexone for Days Retained, Proportion of Heroin-Negative Urine Samples, and Proportion of Heroin-Negative Urine Samples With Missing Samples Imputed as Positive

Outcome Variable	Depot Naltrexone, Mean (SD)	Oral Naltrexone, Mean (SD)	Analysis of Covariance	
			$F_{1,111}$	Adjusted R^2
Days retained in treatment	42.5 (3.3)	31.8 (2.5)	6.49*	0.086
Proportion of heroin-negative urine samples	0.77 (0.06)	0.70 (0.05)	1.00	0.024
Proportion of heroin-negative urine samples (missing samples imputed as positive)	0.52 (0.05)	0.37 (0.04)	5.26*	0.048

[a]Models include participant race, age, and years of regular heroin use as covariates.
*$P < .05$.

Table 3. Full Analysis of Covariance Models Comparing Oral Behavioral Naltrexone Therapy Versus Full-Dose (384 mg) Depot Naltrexone With Cognitive-Behavioral Therapy on Days Retained, Proportion of Heroin-Negative Urine Samples, and Proportion of Heroin-Negative Urine Samples With Missing Samples Imputed as Positive

Outcome Variable	*df*	Mean Square	*F*	*P* Value
Days retained in treatment[a]				
Treatment group	1	3,830.85	11.84	.001
Race	1	1,803.82	5.58	.022
Baseline heroin use	1	10.80	0.03	.856
Treatment group × baseline heroin use	1	2,106.99	6.51	.014
Proportion of heroin-negative urine samples[b]				
Treatment group	1	0.867	7.32	.009
Race	1	0.094	0.71	.379
Baseline heroin use	1	0.000	0.00	.997
Treatment group × baseline heroin use	1	0.693	5.85	.019
Proportion of heroin-negative urine samples (missing samples imputed as positive)[c]				
Treatment group	1	1.321	13.51	.001
Race	1	0.128	1.31	.257
Baseline heroin use	1	0.046	0.47	.497
Treatment group × baseline heroin use	1	0.876	8.96	.004

[a]Error: $df = 53$, mean square = 323.56. Adjusted $R^2 = 0.197$.
[b]Error: $df = 48$, mean square = 0.118. Adjusted $R^2 = 0.077$.
[c]Error: $df = 53$, mean square = 0.098. Adjusted $R^2 = 0.173$.

Injection group patients furnished 62.5% of requested urine samples (mean = 9.48, SD = 4.98 samples); oral group patients furnished only 44.7% of requested urine samples (mean = 7.67, SD = 5.18 samples). Typically, patients across both conditions provided at least 1 urine sample per week until they dropped from treatment, and then all remaining urine samples were missing. The differences between conditions in number of provided urine samples did not reach statistical significance ($t_{109} = 1.81$, $P = .071$). Fifty percent (n = 21) of injection group patients tested positive for opioids during the first 8 weeks in treatment; 90% (n = 19) of those who tested positive had their first heroin-positive urine sample within the first 2 weeks of outpatient treatment. Fifty-five percent (n = 38) of the oral group patients tested positive for opioids during the first 8 weeks in treatment; 87% (n = 33) of those who tested positive had their first positive urine sample within the first 2 weeks of treatment. We also examined the rate of provision of any positive urine sample in the last 2 weeks of treatment (weeks 7 and 8); 8% (2 of 26) of the injection group patients tested positive for opioids during the last 2 weeks of treatment, and 21% (6 of 29) of the oral group patients tested positive in the last 2 weeks. There were no significant differences between injection and oral conditions on proportion of heroin-negative urine samples provided during treatment ($F_{1,106} = 1.00$, $P = .32$). However, when missing urine samples were imputed as positive, injection group patients demonstrated a higher proportion of heroin-negative urine samples ($F_{1,106} = 5.26$, $P = .024$). Again, the interaction between treatment condition and severity of baseline heroin use was included in these 2 analyses but was not found to be significant and so was dropped from the models.

It is noteworthy that patients receiving injectable naltrexone continued to use opiates at approximately the same frequency and speed as patients receiving oral naltrexone. We looked more closely at the individual opiate use patterns of patients who used opiates early in treatment (the first 2 weeks), noting whether those patients went on to complete a full 8-week course of treatment. Forty-seven percent (n = 9) of the injection group patients who used heroin in the first 8 weeks of care went on to complete treatment, while only 27% (n = 8) of the oral/BNT patients who used heroin early in the study completed 8 weeks of care.

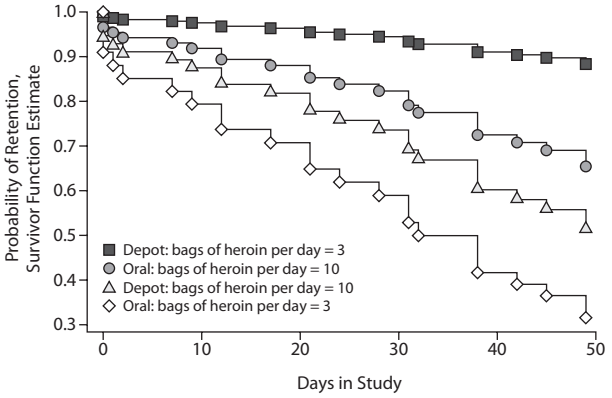
Intensive Psychosocial/Oral Maintenance Therapy vs High-Dose Injection Maintenance Therapy (n = 58)

A second set of analyses comparing oral/BNT (n = 36) to high-dose injection/CBT (n = 22) was undertaken, which also included the interaction between treatment condition and severity of baseline heroin use. These 2 conditions differed from each other on race; patients in the high-dose injection/CBT condition were more likely to be African American (41% in the high-dose injection/CBT group, 19% in the oral/BNT group; $\chi^2_3 = 7.74$, $P = .052$).

Sixty-eight percent of high-dose injection/CBT patients and 53% of oral/BNT patients completed 8 weeks of treatment. Eighty-two percent (18 of 22) of the high-dose injection/CBT patients consented to receive the second dose of injectable naltrexone after 4 weeks; patients not receiving the second dose often dropped from treatment at or just before the 4-week point. High-dose injection/CBT patients remained in treatment for a mean of 47.7 days (SD = 15.8 days), while oral/BNT patients remained in treatment for a mean of 36.6 days (SD = 21.4 days); when we controlled for the impact of race on outcome, this difference was statistically significant ($F_{1,58} = 5.60$, $P = .021$). When the interaction term was added to this equation, it was also significant ($F_{1,58} = 6.51$, $P = .012$); Table 3 shows the full model. Patients with high-severity heroin use remained in treatment longer in the oral/BNT group, whereas those with lower-severity heroin use completed more days of treatment in the high-dose injection/CBT group.

Cox survival analysis models found a significant interaction between treatment groups and baseline severity on

Figure 1. Cox Proportional Hazards Model Estimated Survival Functions Over 8 Weeks of Treatment Demonstrating the Interaction Between Treatment Condition and Baseline Opioid Dependence Severity for Patients Treated With High-Dose Naltrexone Injection and CBT Versus Patients Treated With Oral Naltrexone Maintenance and BNT[a]



[a]Patients were treated with either (1) 384-mg injections of depot naltrexone plus twice-weekly CBT or (2) oral naltrexone (50 mg/d) plus intensive behavioral treatment (BNT). Designations for high (10 bags/day) and low (3 bags/day) severity are ± 1 standard deviation (3.6) from the mean (6.4), rounded to the nearest whole unit.
Abbreviations: BNT = behavioral naltrexone therapy, CBT = cognitive-behavioral therapy.

time to dropout from treatment (likelihood ratio: $\chi^2_1 = 9.31$, $P = .002$). In the oral/BNT group, an increase of 1 bag per day in baseline use was associated with a 14% decrease in the hazard of dropout (hazard ratio = 0.86; 95% CI, 0.73–1.05), while in the high-dose injection/CBT group, a 1-bag-per-day increase in baseline use was associated with a 50% increase (hazard ratio = 1.50; 95% CI, 1.13–2.01) in the hazard for dropout. See Figure 1 for a graphic representation of the Cox model estimate of the survival function based on severity of baseline heroin use, using 3 bags per day and 10 bags per day as representative levels of baseline use (± 1 SD from the mean of bags per day).

High-dose injection/CBT patients furnished 65.9% of requested urine samples (mean = 10.36, SD = 4.44 samples); oral/BNT patients provided 52.3% of requested urine samples (mean = 8.70, SD = 5.20 samples). This difference was not significant ($t_{56} = 1.25$, $P = .216$). Fifty percent of high-dose injection/CBT patients (n = 11) tested positive for opioids during the first 8 weeks in treatment; all but 1 of those patients who tested positive had their first heroin-positive urine sample within the first 2 weeks of outpatient treatment. Fifty-eight percent (n = 20) of the oral/BNT patients tested positive for opioids during the first 8 weeks in treatment; 90% (n = 18) of those who tested positive had their first positive urine sample within the first 2 weeks of treatment. We also examined the rate of provision of any positive urine sample in the last 2 weeks of treatment (weeks 7 and 8); 6% (1 of 16) of the injection group patients tested positive for opioids during the last 2 weeks of treatment, and 17% (3 of 18) of the oral group patients tested positive in the last 2 weeks. There were no significant differences between high-dose injection/CBT and oral/BNT conditions on proportion of heroin-negative urine samples provided during treatment ($F_{1,53} = 1.37$, $P = .25$). When the interaction term between treatment condition and baseline severity was entered, it was statistically significant ($F_{1,53} = 5.85$, $P = .019$); see Table 3 for the full model. Patients with high-severity heroin use were more likely to exhibit less use in the oral/BNT group, whereas those with lower-severity heroin use were more likely to use less in the high-dose injection/CBT group. The same comparison was also analyzed when missing urine samples were imputed as negative. When the interaction term between treatment condition and baseline severity was entered, it was statistically significant ($F_{1,53} = 8.96$, $P = .004$); see Table 3 for the full model. Again, patients with high-severity heroin use were more likely to exhibit less use in the oral/BNT group, whereas patients with lower-severity heroin use were more likely to use less in the high-dose injection/CBT group.

Again, we looked more closely at the individual opiate use patterns of patients who used opiates early in treatment (the first 2 weeks), noting whether those patients went on to complete a full 8-week course of treatment. Seventy percent (n = 7) of the high-dose injection/CBT patients who used opiates in the first 8 weeks of care went on to complete treatment, while only 33% (n = 6) of the oral/BNT patients who used opiates early in the study completed 8 weeks of care.

Adverse Events

The use of naltrexone as an antagonist provokes some concern about safety issues, such as patients attempting to override the antagonist blockade or the risk of overdose. Across all 111 patients reported here, we saw no indication that any patient attempted to override the naltrexone blockade. One patient in the compliance enhancement condition (oral naltrexone combined with minimal psychosocial treatment) did die of an accidental heroin overdose after discontinuing naltrexone and resuming baseline heroin use. This patient presented in week 20 with urine positive for opioids and nonfluorescent for riboflavin, indicating discontinuation of naltrexone, and the patient subsequently overdosed.

DISCUSSION

This quasi-experimental comparison of relatively similar heroin-dependent patients participating in varied conditions of outpatient naltrexone maintenance treatment suggests overall that a long-acting, sustained-release depot formulation of naltrexone may be superior to oral naltrexone for the antagonist treatment of heroin dependence, although it also raises some questions about the robustness of the effect of long-acting naltrexone. When long-acting injectable naltrexone conditions from the Comer et al[11] study were combined and compared to the early combined results from the Nunes et al[6] oral naltrexone maintenance study, patients receiving long-acting injectable naltrexone were retained for more days in treatment. The difference in dropout rate evaluated

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with survival analysis was in the same direction but did not reach significance. When missing urine samples were imputed as positive, the proportion of opioid-negative urine samples was greater for injectable than for oral naltrexone. The difference was not significant when only observed urine samples were counted, but the imputation of missing urine samples as positive is reasonable because most patients who dropout can be assumed to have relapsed.

A second series of analyses compared the group that received an intensive psychosocial treatment (behavioral naltrexone therapy), combining oral naltrexone with numerous and powerful psychosocial strategies, against a moderate psychosocial intervention with a full dose of long-acting injectable naltrexone; this set of analyses was included because it represented the 2 most likely manners in which naltrexone might be used in actual clinical practice. In this comparison with relatively small numbers, injectable naltrexone with moderate treatment retained patients significantly longer than the intensive strategy intended to support oral maintenance therapy. However, when the interaction of baseline heroin severity with treatment condition was included in the model, it was significant, indicating that patients with high baseline heroin use demonstrated better retention on oral naltrexone plus intensive psychosocial intervention, while lower-severity heroin users were more successful in the condition with moderate psychosocial treatment and long-acting injectable naltrexone. Differences in heroin use demonstrated a similar pattern.

The finding of an interaction effect between condition and baseline severity of use should be approached with caution. It is possible that the intensive psychosocial approaches employed in BNT are most needed among individuals with heavy opioid use and that, while the majority of users might be served by moderate psychosocial treatment and implants or injections, patients with high levels of opioid dependence may require more intensive psychosocial treatment. Of course, given the quasi-experimental nature of this research, these findings should be viewed cautiously and should be considered as hypotheses to guide further study. Future research examining long-acting injectable naltrexone in combination with an intensive behavioral regimen similar to BNT in a randomized trial would more definitively measure the value of high-intensity psychosocial treatments.

One of the most interesting findings of this comparison was the relatively similar level of early opiate use by patients across all conditions; approximately 50% of patients used heroin in the first 2 weeks of treatment, regardless of the route of naltrexone treatment. In this respect, high-dose injection (384 mg) showed its promise, as 70% of high-dose injection patients who used opiates early in the study recovered from this use to go on to complete 8 weeks of treatment.

It is also noteworthy that across these 111 patients, we were aware of no patient attempts to override the naltrexone blockade—a common concern about naltrexone, but occurrence seems to be rare, and our experience bears this out. The main concern with naltrexone is overdose risk after the blockade has worn off. Injectable naltrexone may be safer in this respect because the blockade wears off more slowly.

In comparison to other quasi-experimental studies of oral and implant formulations of naltrexone,[13–15] this modestly powered study is the most rigorous comparison to date. The data were collected during the course of randomized clinical trials; consequently, numerous urine samples were collected from patients engaged in treatment, and opiate use results are available over the course of the full 8 weeks of treatment, rather than having to rely on self-report or collateral report. Some groups differed significantly from each other on some key variables, such as age and number of years of regular heroin use; these variables were controlled for during analysis.

All advantages to this comparison noted, the study suffers from some significant limitations. Patients were not randomly assigned to conditions, and significant selection biases are possible. The selection criteria for patients and the background treatment patients received in both trials were very similar, although patients treated at the STARS clinic had some latitude in choosing which treatment study to participate in. (If anything, the bias in patient selection favors the oral naltrexone study versus the injectable naltrexone study for 2 reasons: patients in the oral naltrexone study were required to have a significant other who was willing to participate in treatment [indicating a certain level of social support and functioning], and half of the injection patients were on a lower, less powerful dose of medication.) Furthermore, these treatments were not originally intended to be compared to one another, so there may be differences that cannot be accounted for. We do not have follow-up data on patients who dropped from treatment early in the study and so can only presume relapse to heroin use for those individuals (the most typical course when patients have been recently detoxed and are not maintained on medication). Finally, while other opiate users were not excluded, we have only heroin users in these samples because this is how the recruitment advertising was worded; further studies with prescription opiate users are needed to assess the effectiveness of these approaches with other opioids of abuse.

Given these limitations, these results should be interpreted with caution and viewed as exploratory for the purposes of informing the hypotheses of future research studies, as well as to help manage practitioners' expectations when working with oral and injectable naltrexone. However, despite these limitations, the differences between high-dose long-acting injectable formulations and other oral maintenance strategies are intriguing. This quasi-experimental study of early outcomes in naltrexone maintenance strategies demonstrates some benefit to long-acting injectable formulations but also shows that heroin use behavior during maintenance treatment is relatively similar despite route of naltrexone administration; this finding is not surprising, as retention in treatment is the more important outcome in maintenance treatment. If opioid-dependent patients are able to stay on naltrexone treatment, opioid-taking behavior is quite likely to extinguish due to the powerful blockade of opioid-reinforcing effects. Furthermore, contingent on

future replication, the findings of this study also indicate that, despite the development of new formulations of naltrexone, the value of intensive psychosocial approaches may continue to be demonstrated for severe users. It is possible that combining monthly injections with some of the strategies that have maximized oral compliance (high-value vouchers, significant-other involvement) could further increase the effectiveness of long-acting injectable naltrexone maintenance therapy and position this treatment as a viable alternative to agonist maintenance therapy (buprenorphine or methadone) for some opioid-dependent patients. There is a need for continued studies that would determine the optimal strategies for combining psychosocial approaches with the new long-acting injectable formulations of naltrexone to yield maximal effectiveness.

Drug names: buprenorphine (Buprenex, Subutex, and others), methadone (Methadose, Dolophine, and others), naltrexone (Vivitrol, ReVia, and others), naltrexone extended-release intramuscular depot formulation (Depotrex, Vivitrol, and others).

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Potential conflicts of interest: **Dr Comer** has been a consultant to Purdue Pharma, Alpharma, King, Inflexxion, Shire, BioDelivery Services, and Analgesics Research; has received grant/research support from Schering-Plough, Grünenthal GmbH, Reckitt Benckiser, and Johnson & Johnson; has received honoraria from the Rehabilitation Institute of Chicago, Yale University, Wake Forest University, and the University of Michigan at Ann Arbor; and has served on the speakers or advisory boards of Alpharma and King. **Dr Bisaga** has received a grant from Alkermes to conduct a study of depot naltrexone in a clinical trial; Alkermes is providing the medication. **Dr O'Brien** has an ongoing intermittent consulting relationship with Alkermes. **Dr Nunes** served on the board of Alkermes/Cephalon until he resigned from that position in November of 2007. Alkermes/Cephalon makes a comparable product to Depotrex, the product used in this study. **Drs Brooks**, **Sullivan**, **Carpenter**, **Raby**, and **Yu** have no conflicts to disclose that could affect the reporting of this study.

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