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Accounting for the uncounted: Physical and affective distress in individuals dropping out of oral naltrexone treatment for opioid use disorder*

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Abstract

Background: The theoretical benefits of naltrexone as a treatment for opioid use disorder (e.g., safety, non-addictive, low risk of diversion) stand in sharp contrast to its disappointing record on retention in most samples. The relationship of uncomfortable physical and dysphoric symptoms to retention on naltrexone is a controversial and under-studied issue.

Methods: Using data from a randomized controlled trial of voucher-based contingency management and support from a significant other to enhance retention on oral naltrexone, we compared self-reported somatic and dysphoric symptoms, measured weekly, for individuals who were retained on naltrexone through the 12-week trial (n=50) versus those who dropped out (n=70).

Results: There were no differences between participants who completed treatment and those who dropped out on multiple baseline characteristics, including somatic or affective symptoms prior to treatment. However, whether analyzed cross-sectionally or over time, participants who dropped out consistently reported higher rates of somatic symptoms, particularly difficulty sleeping, as well as affective symptoms, including multiple indicators of depression, anxiety, and anhedonia.

Conclusions: Although the smaller group of participants who were retained on oral naltrexone for 12 weeks reported decreasing physical and affective discomfort over time, there was

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KMC, CN, and MS designed the study and analyses. TLF and CN conducted the analyses. All authors contributed to, reviewed, and approved the manuscript as submitted

Conflict of Interest

No conflict declared.

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substantial evidence that those who dropped out experienced continued and significant levels of distress. Individuals who report physical or affective distress while taking naltrexone may be at higher risk of dropout.

Keywords

Naltrexone; Retention; Anhedonia; Adverse Events; Opioids; Heroin

1. Introduction

Multiple strategies are needed to address the current opioid epidemic and improve response to approved medication assisted treatments (MAT) for opioid use disorder (OUD) (Volkow, 2018). While buprenorphine, methadone, and naltrexone all have their strengths and weaknesses, the great potential of naltrexone, in particular, has been undercut by difficulties with induction and retention (Kirchmayer et al., 2002; Larney et al., 2014; Sullivan et al., 2017). The advent of extended-release injectable naltrexone (XR-NTX) held promise for improving adherence, but recent reviews indicate that adherence to XR-NTX remains disappointing across several populations; 1 is the modal number of injections in community settings (Jarvis et al., 2018; Morgan et al., 2018).

Similar to the more extensive literature on oral naltrexone (reviewed in Kirchmayer et al., 2002; Larney et al., 2014), the recent Jarvis systematic review of XR-NTX induction and retention rates from 34 randomized clinical trials and observational studies in a range of populations with opioid use disorder (OUD) suggested wide variability in retention across settings and samples, with 6-month retention rates as low as 10.5% (Cousins et al., 2016). Not surprisingly, rates of retention are substantially higher in samples of health professionals (up to 75% through 6 months) (e.g., Earley et al., 2017) and criminal justice populations (e.g., Coviello et al., 2010; Lee et al., 2016), who risk significant negative consequences for relapse. Studies that circumvent the 'induction hurdle', for example, by starting injections while participants are still in prison (Friedmann et al., 2018; Gordon et al., 2015; Lincoln et al., 2018) or inpatient settings (Lee et al., 2018) have higher rates of induction but low rates of retention nonetheless (seldom higher than 30% in prisoners, 50% in non-prison populations) (Jarvis et al., 2018). Despite the high risks of relapse and overdose that follow dropout from naltrexone (Gibson and Degenhardt, 2007; Kelty and Hulse, 2012; Miotto et al., 1997), relatively few studies have assessed factors that may be associated with dropout from naltrexone treatment (Friedmann et al., 2018; Nunes et al., 2015).

Most evidence suggests only a minority of patients stay on naltrexone, even with the advent of long-acting injectables or after initiating treatment well after resolution of withdrawal symptoms (e.g., after hospitalization or in prison). There are multiple potential reasons, including flagging motivation to remain abstinent, lack of reinforcing effects of taking naltrexone (compared with agonist medications), and absence of withdrawal upon stopping treatment. However, the adverse effects of naltrexone itself, which are often difficult to distinguish from symptoms of protracted withdrawal from opioids and most notably include symptoms of negative affect, dysphoria, and anhedonia associated with the so-called

‘naltrexone flu’ (Rounsaville, 1995; Sullivan et al., 2015; Williams et al., 2017), remain understudied.

The presence and severity of negative affective states associated with naltrexone is controversial. Animals who have experienced naltrexone-precipitated opioid withdrawal demonstrate conditioned place aversion and acoustic startle (i.e., anxiety-like behavior) for extended periods of time (Rothwell et al., 2012; Stinus et al., 2000). In humans, multiple studies have shown that opioid-naïve individuals find naltrexone aversive (Hollister et al., 1981; Mendelson et al., 1978). While naltrexone effectively blocks subjective effects from opioids and to a lesser extent from alcohol (Bigelow et al. 2012), it does not alter the subjective-rewarding effects of smoked cocaine, oral amphetamine, or oral or intravenous 9-tetrahydrocannabinol (THC) (Comer et al., 2013; Ranganathan et al., 2012; Wachtel and DeWitt, 2000). In non-opioid using samples, naltrexone attenuates reward from pleasurable activities such as exercise or music (i.e., anhedonia) (Daniel et al., 1992; Mallik et al., 2017). In contrast, a recent study of naltrexone did not alter the positive social stimuli and slowed identification of negative stimuli (i.e., anxiolytic effects) in healthy controls (Wardle et al. 2016). These contradictory effects of naltrexone have been attributed to the balance between its “antireward” mu-opioid blocking and “anxiolytic” kappa- opioid blocking effects (Wardle et al. 2016).

Among opioid-dependent individuals retained on naltrexone, reports suggest that the presence and severity of somatic or dysphoric symptoms diminish over time: Dean and colleagues (2006) reported reduced Beck Depression (BDI) (Beck et al., 1961) scores among 9 (of 42) participants who were fully adherent to naltrexone in a 6-month trial. Baseline BDI scores did not distinguish those who were adherent from those who dropped out of treatment; however, at all follow-ups, BDI scores were significantly higher in the non-adherent group. In a sample of 34 individuals who completed at least 4 weeks of outpatient depot naltrexone maintenance, dysphoric symptoms decreased over time, but sleep impairment increased (Mysels et al., 2011). These data are consistent with many studies reporting on somatic and affective symptoms in indicating that these symptoms decrease over time for those who remain in treatment, leading to the overall conclusion that naltrexone treatment does not cause negative affect (reviewed in Miotto et al., 2002).

In contrast, few studies have reported on somatic or affective symptoms in the majority of individuals who drop out of naltrexone treatment for OUD. Krupitsky and colleagues assessed depression, anxiety, and anhedonia in a large (N=306) sample of individuals randomized to oral naltrexone, naltrexone implants, or placebo (Krupitsky et al., 2016). There were significant reductions in these symptoms over time among the 34% of individuals assigned to either form of naltrexone (oral or implants) who were retained for 6 months. While a series of cross-sectional analyses comparing scores on these measures at monthly intervals by retention status (completers compared with the final report obtained for those who dropped out) indicated few significant differences between groups, it was difficult to relate reported symptoms to time of dropout, as symptoms of depression, anxiety, and anhedonia were measured infrequently, and sample sizes obtained for those who dropped out were small.

Thus, while multiple studies indicate that individuals retained on oral and implantable naltrexone report reduced physical and affective symptoms over time, there has been little focus on the experiences of those who leave naltrexone treatment, particularly in terms of symptoms of opioid withdrawal as well as somatic or affective adverse effects. To address this gap, we compare somatic and affective symptoms collected on a weekly basis from participants enrolled in a randomized clinical trial of 12-week oral naltrexone for OUD (Carroll et al., 2001). We hypothesized that both types of symptoms would be higher among those who dropped out of treatment.

2. Methods

2.1. Summary of parent clinical trial

This report is a secondary analysis of a randomized controlled trial of oral naltrexone and behavioral interventions, described in detail in the main study report (Carroll et al., 2001).

Briefly, individuals who completed either an inpatient or outpatient opioid detoxification were randomized to one of three conditions in conjunction with standard naltrexone treatment at a primary care center (3× week naltrexone, 3× week urine specimen collection, weekly group therapy): 1) no additional behavioral intervention (standard naltrexone), 2) voucher-based contingency management (CM) for ingesting naltrexone in the presence of the study nurse and submitting urine specimens negative for opioids and stimulants (maximum potential total value earned=\$561), or 3) voucher based reinforcement with the same maximum potential value plus weekly structured family/significant other sessions (up to 6 sessions, CM+family). The vouchers were intended to address naltrexone's lack of immediate reinforcement; the significant other sessions were intended to provide social support and motivation for continuing naltrexone treatment. Individuals were included who were 18 or older, met current DSM-IV criteria for opioid dependence, were determined to be appropriate for naltrexone (e.g., liver function tests no higher than three times normal, not pregnant, did not meet criteria for bipolar or schizophrenic disorder), and had a significant other (usually a parent, sibling, or spouse/partner) who was willing to participate in the weekly manual-guided sessions.

Primary study analyses were conducted on the intention to treat sample (N=127); 12-week outcome data were collected from the 50 individuals who completed the trial (took naltrexone all 12 weeks), 62 (86%) of the 72 individuals who dropped out of treatment, and 2 (40%) of the 5 individuals who were randomized but did not initiate naltrexone treatment. For this report we include data from the 50 completers and 70 non-completers (excluding the 5 participants who did not initiate treatment and 2 individuals who began naltrexone treatment but dropped out in the first week prior to completing any reports on symptoms).

Primary outcome analyses were conducted using random regression analyses with two contrasts. One evaluated the effects of CM (CM plus CM+family versus standard naltrexone); the other evaluated the effects of family involvement (CM+family versus CM). Results indicated statistically significant effects for CM versus no CM on retention ($p=.05$), medication adherence ($p=.05$), and opioid-negative urine specimens ($p=.02$). There were significant effects of family involvement on these outcomes only for the subgroup who

completed at least one family session (Carroll et al., 2001). Completion rates for the 12-week trial were lowest in standard naltrexone (25.6%) and significantly higher in both conditions offering CM (42.9% in CM; 47% in CM+family). There was one participant death from an overdose in the follow-up phase of the study.

2.2. Assessments

Structured Clinical Interviews for DSM-IV (SCID) (First et al., 1995) were conducted at baseline to assess DSM-IV disorders. The Timeline FollowBack method (Robinson et al., 2014) was used to collect day-by-day reports of all types of substance use for both the 28-day period prior to baseline assessment and the 12-week treatment period. Urine specimens were collected three times weekly and at each follow-up interview. Symptoms of opioid withdrawal were assessed weekly using an 18-item scale used in previous naltrexone and opioid detoxification studies in this setting (O'Connor et al., 1997; O'Malley et al., 1992; Rounsaville, 1985), in which participants rated each symptom on a 0–3 scale (0=none, 1=mild, 2=moderate, 3=severe). The Brief Symptom Inventory (BSI) (Derogatis and Melisaratos, 1983) was completed weekly by participants to assess a range of psychiatric symptoms. As a measure of anhedonia was not included in the parent study, we identified one item from the Depression scale of the BSI, “feeling no interest in things”, as a proxy for anhedonia. The BDI (Beck et al., 1961) was completed weekly by participants, and the Hamilton Depression Rating Scale (Ham-D; Bech et al., 2015) was completed monthly by the study nurse.

2.3. Data analyses

Baseline demographic and drug use differences between individuals who completed the 12-week trial and those who dropped out were evaluated via chi-square tests for categorical variables and *t*-tests for continuous variables. Somatic and affective symptoms experienced in the week prior to termination were evaluated using chi-squares and general linear models with treatment completion as the independent variable. To evaluate symptoms over time leading up to treatment termination, weekly somatic and psychological distress scores (BSI, BDI, the ‘anhedonia’ item) prior to treatment termination were evaluated using multilevel longitudinal mixed effect regression models. Each multilevel longitudinal model included treatment endpoint and all raw data collected in the 4 weeks preceding termination as the observations nested within participants, with treatment endpoint as the intercept and termination week minus 1 as time point 1, termination week minus 2 as time point 2, etc. Treatment condition, treatment completion status, and time were the independent variables, and the intercept was the only random effect. For simplicity, the findings for the random effect models using treatment completion status and time are presented in the Supplemental Material¹. Finally, all analyses evaluating differences in symptoms by treatment condition (CM or family involvement) were non-significant and hence not presented here (available on request).

¹Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

3. Results

3.1. Participant baseline characteristics by completer status

Table 1 presents baseline demographic and substance use characteristics, rates of DSM-IV psychiatric disorders, and baseline scores on indices assessing somatic and affective symptoms by completer status (70 treatment terminators versus 50 treatment completers). Noncompleters were significantly younger than completers. Otherwise, there were no statistically significant differences between the completers and treatment terminators on any baseline demographic or substance use variables tested, nor were there any significant differences in any somatic or affective symptom measure at baseline. Table 1 also shows treatment adherence and primary study outcomes by completer status. As expected, completers had significantly better outcomes for all retention-related outcomes, including weeks in treatment, naltrexone doses, urine specimens negative for all drugs tested, and self-reported days of abstinence (all $p < .01$).

3.2. Somatic symptoms, cross-sectionally and longitudinally

Rates of opioid withdrawal symptoms or adverse events associated with naltrexone treatment in the participants' week prior to termination, by completer status, are shown in Table 2. Early terminators had significantly higher symptom prevalence with difficulty sleeping, sneezing, muscle pain, sweating, and chills as the most endorsed symptoms. The mean total number of symptoms endorsed in the participant's last week of treatment was 4.9 ($sd=5.4$) for treatment terminators versus 0.8 ($sd=1.8$) for completers ($t(1, 118)=5.18$, $p < .001$) with a range of 0 to 18.

The cross-sectional analyses described above represent all data collected from the participants but reflect assessment of symptoms collected at different times (i.e., week 12 of treatment for completers versus last week before dropout for non-completers). The pattern of ratings across time are shown in Figure 1, where mean symptom severity scores steadily decline over time for the completers. In contrast, while symptom severity scores for noncompleters and completers were initially similar, differences in symptom severity emerge around week 5 and increase until dropout. These patterns for mean withdrawal symptom count as well as for individual items (e.g., insomnia); there were significantly higher scores for non-completers versus completers on all variables tested. The two indicators of affective symptoms associated with protracted withdrawal and/or naltrexone (nervousness/restlessness and 'feeling blah') showed the same pattern.

Finally, somatic symptom scores were evaluated over time in multilevel longitudinal mixed effect models that included data from the week of dropout and the preceding 4 weeks using completer status, time, and their interaction as independent variables. These models indicated that, overall, the mean total severity ratings were significantly higher at treatment termination and in the four preceding weeks for participants who dropped out of treatment compared to those who completed treatment (main effects of completer status, $F(1, 106)=21.46$, $p < .01$). There was a significant interaction of completer status and time ($F(1, 203)=15.24$, $p < .00$); participants who completed treatment had a greater rate of reduction in symptoms prior to termination than participants who dropped out.

3.3. Affective symptoms, cross sectionally and longitudinally by completer status

Table 3 presents BSI, BDI, Ham-D scores, and the ‘anhedonia’ item at the last timepoint assessed (end of treatment for completers; week prior to dropout for treatment terminators). As with the somatic symptoms, there are statistically significant differences by completer status for all measures, including the BSI Positive Symptom Index and all subscales, as well as BDI, HAM-D scores, and the anhedonia item. Seen across time in Figure 2, as with the somatic symptoms, affective symptoms start at similar levels for both groups and drop steadily over time for the completers but begin to separate around week 3 and remain elevated through the 12-week end of treatment assessment for the noncompleters.

The second row in Figure 2 further distinguishes participants who dropped out, with black bars for those who dropped out in the next week and grey bars for those non-completers who persisted in treatment at least one more week. These suggest some patients left treatment after the peak of that symptom, but many persisted for several weeks with elevations in these symptoms but nonetheless dropped out eventually.

Finally, affective distress scores were evaluated over time in multilevel longitudinal mixed effect models that included data from the week of dropout and the preceding 4 weeks using completer status, time, and their interaction as independent variables. These models indicated that, overall, each of the affective distress scores was significantly higher at treatment termination and in the four preceding weeks for participants who dropped out of treatment compared to those who completed treatment (main effects of completer status: BDI total score $F(1, 131) = 25.59, p < .01$, BSI general $F(1, 131) = 17.01, p < .01$, BSI anhedonia item $F(1, 146) = 11.69, p < .01$).

4. Discussion

This is the first study to evaluate self-reported somatic and affective symptoms cross-sectionally and over time in a relatively large sample of individuals on oral naltrexone treatment, comparing symptoms assessed on a weekly basis for those who completed treatment versus those who dropped out. There were no statistically significant differences between the groups on any somatic or affective symptoms at baseline, but virtually all symptoms assessed at treatment termination and in the weeks preceding termination were significantly higher for participants who dropped out of treatment. In terms of somatic symptoms, there were particularly elevated rates of difficulty sleeping, nervousness, restlessness, and feeling ‘blah’. For affective symptoms, there were elevations in most domains, including depression, anxiety, and the proxy measure of anhedonia, and the non-completers showed elevated scores compared to completers in the weeks prior to dropout. These data are consistent with the existing literature on naltrexone in pointing to steadily decreasing discomfort over time for individuals who remain on naltrexone for a full course of treatment (Miotto et al., 2002). Thus, those who persisted in treatment tolerated naltrexone well and showed steady improvements in somatic and affective symptoms over time.

Conversely, our data suggest that the larger group of participants who dropped out of treatment reported sustained somatic and affective symptoms to baseline relative to

treatment completers. This occurred in all areas and symptoms assessed and regardless of whether symptoms were assessed cross-sectionally or longitudinally. Thus, at least some individuals taking naltrexone experienced no improvement of these of symptoms over time; this may signal imminent dropout.

Several factors have been suggested as reasons for high attrition within samples of OUD maintained on naltrexone; 'feeling cured' is among them (Williams et al., 2017). However, sustained somatic or affective discomfort is seldom acknowledged as a reason for dropout. Our data suggest otherwise, at least in this sample of individuals taking naltrexone orally. Somatic and dysphoric symptoms, whether associated with naltrexone treatment itself, protracted withdrawal, or other factors yet to be identified, appears to be a significant issue that may be associated with the disappointing rates of retention in naltrexone treatment. While the Jarvis et al. (2018) review indicates that although 6-month rates of retention in studies of long-acting depot formulations of naltrexone are better than those of oral naltrexone, retention rates are still disappointing and seldom over 40% at 6 months in general populations. Hence, efforts to assess symptoms of patient discomfort are warranted in such studies. It is also of note that, of the studies included in the Jarvis review, only a handful reported that they assessed symptoms of withdrawal or dysphoria (Bisaga et al., 2014, 2015; Gordon et al., 2015; Lee et al., 2016, 2018; Sullivan et al., 2015, 2017; Tanum et al., 2017). In these studies, symptoms assessed consistently diminished over time for those who completed treatment, yet none of these reported on symptoms among individuals who did not complete treatment.

The data presented here also suggest that there may be some individuals who tolerate naltrexone treatment better than others. This is consistent with the literature pointing to individual differences in response to opioids as well as severity and duration of withdrawal symptoms in OUD (Eap et al., 2002; Huhn et al., 2016; Rounsaville et al., 1985). Characteristics of individuals who differ in their reports of unpleasant somatic or affective symptoms could not be discerned from these data, as none of the large number of baseline demographic (other than age), substance use history, psychiatric, or baseline variables assessed distinguished completers from noncompleters. Individuals who dropped out of naltrexone treatment did not report significantly higher levels of somatic symptoms, dysphoria, or anxiety at baseline, nor did they have higher rates of psychiatric disorders. This is consistent with the extant literature, which has not pointed to any specific demographic, psychiatric, or environmental predictors of response to naltrexone (Friedmann et al., 2018; Nunes et al., 2015). Thus, the field may need to look beyond the 'low-hanging fruit' of routinely-measured baseline characteristics in identifying predictors of optimal response to the various forms of MAT. Continued efforts to identify individual predictors of continued physical or emotional discomfort with naltrexone treatment over time is thus of high significance so that appropriate interventions can be developed or implemented for those at risk of sustained discomfort (e.g., interventions for depression or sleep, additional support).

These data make a strong case for routinely assessing somatic and affective symptoms in individuals with OUD maintained on naltrexone, as continued or increased symptoms may signal risk for imminent attrition. If clinicians or researchers do not attend to these issues,

the bulk of individuals treated with naltrexone are likely to continue to go on ‘voting with their feet’ by dropping out of naltrexone treatment prematurely. Given the high cost associated with detoxification prior to starting naltrexone and the cost of the medication itself, the potential expense of continued monitoring and intervention with naltrexone patients who may be struggling may be justified. Moreover, given the substantial risk of relapse, overdose, and death among individuals who dropout of naltrexone treatment, ignoring such symptoms is clinically unwise.

To our knowledge, this is the first study to report on weekly data from wide range of physical and affective symptoms in a comparatively large sample of individuals with opioid dependence taking naltrexone in the context of a well-controlled randomized trial. High rates of contiguous pre-termination data availability up to and including the point of termination is also a strength. In terms of limitations, the study involved oral naltrexone and may not generalize to groups of individuals taking long-acting injectable formulations. In addition, it was not possible to determine whether symptoms reported by participants reflected symptoms of protracted withdrawal from opioids, adverse effects of naltrexone itself, or other factors. Moreover, as drug use within the trial was confounded with dropout status, it was not possible to disentangle reported physical and affective symptoms from illicit drug use, which also increased prior to dropout. Finally, it should be noted that this was a secondary, largely descriptive analyses of a trial completed several years ago; future studies might more systematically study timing and severity of somatic and affective symptoms using approaches such as ecological momentary assessment (EMA) to more closely link presence, timing, and severity of these and similar symptoms to retention in naltrexone.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Naltrexone treatment studies report decreasing adverse effects/affective symptoms.
- Reports tend to be limited to the minority of participants who are retained.
- Dropouts reported high levels of dysphoria and unpleasant physical symptoms.
- Continued affective or physical symptoms may signal risk for dropout.

Figure 1:

Total withdrawal severity scores over time, non-completers versus completers up to week of dropout. x-axis=weeks in treatment; y-axis=mean withdrawal severity score (maximum=54); higher scores indicate higher severity. Left panel: completers (n=50, line), non-completers (n varies by week, bars). Right panel: completers (n=50, line), non-completers who left in the subsequent week are shown in black bars, non-completers who remained at least one more week shown in grey bars. N's for noncompleters are shown above the bars.

Figure 2:

Mean Brief Symptom Index total positive symptoms (maximum=54), BSI anhedonia item (maximum=3), and Beck Depression Inventory (BDI) (maximum=39) scores by time and completer status. Higher scores indicate greater severity. Top set of panels: line indicates completers (n=50); bars indicate non-completers. Bottom set of panels: Line indicates completers (n=50), black bars indicate participants who dropped out in the following week, grey bars indicate participants who dropped out in a subsequent week. N's for noncompleters are identical to those in Figure 1.

Table 1. Baseline demographic, substance use, withdrawal severity and psychiatric symptomology by completer status.

Variable	Dropouts N=70			Completers N=50			Total N=120			Statistics		
	mean or number	sd or %		mean or number	sd or %		mean or number	sd or %		t or χ^2	df	P
Age	30.6	7.3		35.3	8.5		32.5	8.1		3.25	1,118	.00
Number (%) female	18	25.7		12	24		30	25		0.05	1	.83
Number (%) African American	10	14.3		6	12		16	13.3		1.63	3	.65
(%) Hispanic	4	5.7		3	6		7	5.8				
(%) Caucasian	54	77.1		41	82		95	79.2				
(%) other	2	2.9		0	0		2	1.7				
Number (%) unemployed	39	55.7		21	42		60	50		2.19	1	.14
Number (%) on probation or parole	12	17.4		9	18		21	17.6		0.01	1	.93
Number (%) with less than high school education	12	17.1		8	16		20	16.7		5.04	2	.08
with high school education/GED	27	38.6		29	58		56	46.7				
with some college or higher degree	31	44.3		13	26		44	36.7				
Number of 'bags' of heroin per day	2.9	1.8		2.8	1.4		2.9	1.6		.34	1,115	.73
Days of opioid use/past 28 days per Timeline Follow-back	20.6	7.3		20.3	6.5		20.5	7		0.16	1,115	.87
Days of cocaine use/past 28	4.8	7.7		4.1	7		4.5	7.5		0.54	1,116	.59
Days of alcohol use/past 28	4.6	6.7		4.9	7.7		4.7	7.1		0.20	1,117	.84
Years regular opioid use	5	5.5		5.5	6.5		5.2	5.9		0.42	1,118	.68
Number of previous outpatient treatment episodes	0.87	1.3		0.73	1		0.81	1.2		0.62	1,114	.54
Number of previous methadone treatment episodes	0.22	0.42		0.23	0.42		0.22	0.42		0.15	1,115	.88
Number of previous naltrexone treatment episodes	0.1	0.3		0.19	0.39		0.14	0.35		1.33	1,115	.19
Number of number previous opioid detoxifications	0.9	1.7		1.1	2.6		1	2.1		0.62	1,114	.54
Number (%) meeting lifetime DSM-IV criteria ^a												
Cocaine abuse or dependence	33	64.7		32	66.7		65	65.7		0.04	1	.84
Alcohol abuse or dependence	27	52.		33	68.8		60	60.6		2.59	1	.11
Affective disorder	6	11.8		5	10.4		11	11.1		0.05	1	.83

Variable	Dropouts N=70		Completers N=50		Total N=120		Statistics		
	mean or number	sd or %	mean or number	sd or %	mean or number	sd or %	t or X ²	df	P
Anxiety disorder	3	5.9	5	10.4	8	8.1	0.68	1	.41
Antisocial personality disorder	10	20	5	11.1	15	15.8	1.41	1	.24
<i>Somatic Symptoms</i>									
Mean withdrawal symptom severity (max=54)	13.7	11.1	15.3	10.7	14.4	10.9	0.5	1,115	.45
<i>Affective Symptoms</i>									
Brief Symptom Inventory (BSI) total (max=212)	57.6	43.1	47.2	33.2	53.3	39.5	1.44	1,118	.15
BSI item 18 'anhedonia' (max=4)	1.5	1.3	1.3	1.2	1.4	1.3	0.74	1,118	.46
Beck Depression Inventory (max=39)	10	6.6	8.4	5	9.2	5.9	1.37	1,105	.17
Number of opioid withdrawal sx's (max=18)	8.1	5.2	8.83	4.8	8.4	5	0.73	1,115	.47
<i>Treatment adherence and outcome measures</i>									
Number of weeks in treatment (maximum=12)	3.8	3.1	12	0.2	7.2	4.7	18.84	1,118	.00
Number of naltrexone doses (maximum=36)	8.7	7.9	32.2	6.8	18.5	13.8	17.44	1,118	.00
Number of drug-free urine specimens (max=36)	4.5	6.5	27.4	10	14	13.9	15.12	1,118	.00
Maximum days of abstinence from opioids	21.2	21.2	82.2	2.9	47.7	34.3	20.18	1,113	.00
Percentage of days opioid abstinence (self-report)	78.2	23.9	98.7	2.5	86.9	20.8	6.01	1,116	.00

^aFrom SCID interviews

Table 2.

Percent of participants reporting physical symptoms, week prior to treatment termination, by completer status.

	Dropouts		Completers		Total			
	N=70		N=50		N=120			
Symptom	n	%	n	%	n	%	χ^2	<i>P</i>
Loss of appetite, yes	25	35.7	5	10.0	30	25.0	10.29	.00
Diarrhea	15	21.4	0	0.0	15	12.5	12.25	.00
Sweating	19	27.1	1	2.0	20	16.7	13.28	.00
Joint pains	18	25.7	2	4.0	20	16.7	9.90	.00
Difficulty sleeping	38	54.3	7	14.0	45	37.5	20.20	.00
Muscle pain	26	37.1	3	6.0	29	24.2	15.44	.00
Chills	19	27.1	1	2.0	20	16.7	13.28	.00
Tremors	11	15.7	1	2.0	12	10.0	6.10	.01
Hot flashes	14	20	0	0.0	14	11.7	11.32	.00
Runny nose	28	40	3	6.0	31	25.8	17.60	.00
Tearing	12	17.1	1	2.0	13	10.8	6.92	.01
Stomach cramps	17	24.3	4	8.0	21	17.5	5.36	.02
Yawning	17	24.3	1	2.0	18	15.0	11.36	.00
Nausea	13	18.6	2	4.0	15	12.5	5.66	.02
Dry mouth	13	18.6	3	6.0	16	13.3	3.99	.05
Vomiting	6	8.6	0	0.0	6	5.0	4.51	.03
Sneezing	23	32.9	1	2.0	24	20.0	17.36	.00
Palpitations	11	15.7	2	4.0	13	10.8	4.14	.04
<i>Affective symptoms</i>								
Nervousness/restlessness	29	41.4	6	12.0	35	29.2	12.23	.00
Feeling 'blah'	28	40	3	6.0	31	25.8	17.60	.00

Table 3.

Affective symptoms in the week prior to treatment termination, by completer status.

	Dropouts N=70 ^a		Completers n=50		Total n=120		Statistics		
	<i>mean</i>	<i>sd</i>	<i>mean</i>	<i>sd</i>	<i>mean</i>	<i>sd</i>	<i>t</i>	<i>df</i>	<i>P</i>
BSI Positive Symptom Index (max=53)	13.80	14.30	3.60	7.00	9.50	12.80	4.69	1,117	.00
Somatization (max=4)	0.42	0.73	0.06	0.16	0.27	0.59	3.47	1,117	.00
Obsessive/Compulsive	0.54	0.74	0.17	0.40	0.38	0.64	3.24	1,117	.00
Interpersonal sensitivity	0.43	0.84	0.10	0.33	0.29	0.69	2.72	1,117	.01
Depression	0.55	0.86	0.10	0.27	0.36	0.71	3.54	1,117	.00
Anxiety	0.44	0.72	0.08	0.17	0.29	0.58	3.51	1,117	.00
Hostility	0.45	0.71	0.08	0.45	0.30	0.64	3.21	1,117	.00
Phobic anxiety	0.27	0.59	0.05	0.17	0.18	0.47	2.57	1,117	.01
Paranoid ideation	0.36	0.63	0.11	0.26	0.26	0.52	2.70	1,117	.01
Psychoticism	0.40	0.69	0.08	0.26	0.27	0.57	3.09	1,117	.00
BSI Item 18: Anhedonia	0.55	0.98	0.16	0.62	0.39	0.87	2.49	1,117	.01
Beck Depression Inventory (max=39)	6.34	0.50	1.72	2.85	4.32	5.69	4.69	1,112	.00
Hamilton Depression Rating Scale (max=84)	12.06	6.04	6.06	4.08	9.56	6.07	6.09	1,118	.00

^aSample size varies for dropouts due to failure of some participants to complete measures; n's for dropouts are 69 for BSI Positive Symptom index and subscores, 64 for Beck Depression Inventory, and 70 for Hamilton Depression Rating Scale