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ANHEDONIA, DEPRESSION, ANXIETY, AND CRAVING FOR OPIATES IN OPIATE DEPENDENT PATIENTS STABILIZED ON ORAL NALTREXONE OR AN EXTENDED RELEASE NALTREXONE IMPLANT

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Abstract

Background—Naltrexone is a μ-opioid receptor antagonist that blocks opioid effects. Craving, depression, anxiety, and anhedonia are common among opioid dependent individuals and concerns have been raised that naltrexone increases them due to blocking endogenous opioids. Here we present data that addresses these concerns.

Objective—Assess the relationship between affective responses and naltrexone treatment.

Methods—Opioid dependent patients (N=306) were enrolled in a three cell (102ss/cell) randomized, double blind, double dummy, placebo-controlled 6-month trial comparing extended release implantable naltrexone with oral naltrexone and placebo (oral and implant). Monthly assessments of affective responses used a Visual Analog Scale for opioid craving, the Beck Depression Inventory, Spielberger Anxiety Test, and the Ferguson and Chapman Anhedonia Scales. Between group outcomes were analyzed using mixed model analysis of variance (Mixed ANOVA) and repeated measures and the Tukey test for those who remained and treatment and did not relapse, and between the last measure before dropout with the same measure for those remaining in treatment.

Results—Depression, anxiety, and anhedonia were elevated at baseline but reduced to normal within the first 1-2 months for patients who remained in treatment and did not relapse. Other than

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a slight increase in two anxiety measures at week two, there were no significant between group differences prior to treatment dropout.

Conclusion—These data do not support concerns that naltrexone treatment of opioid dependence increases craving, depression, anxiety or anhedonia.

INTRODUCTION

The Food and Drug Administration approved naltrexone for opioid dependence in 1984 on the basis of its ability to block agonist effects at μ-opioid receptors [Kleber, 2007]. Many thought it would be an effective treatment since one 50 mg tablet blocked opioid effects for 24-36 hours, but early studies did not support this hope. Patients had to be detoxified and free of physiologic dependence to start naltrexone, which was not always easy, but the main problem was that most heroin dependent individuals were not interested in antagonist treatment or dropped out and relapsed after they started it. Exceptions were patients with strong external pressure for abstinence such as impaired health care professionals or those in criminal justice systems who were threatened with incarceration if they used [Kleber, 2007]. Voucher-based incentives [Preston et al, 1999], used alone or with involvement of significant others [Carroll et al, 2001] improved adherence, but the effects were usually modest [Nunes et al, 2006]. Exceptions were in Russia where studies showed more interest in naltrexone with better retention and outcomes than in the U.S. Potential cultural factors contributing to these differences include the fact that Russian law prohibits use of agonists for detoxification or maintenance, patients and their families know that naltrexone is the only available effective medication, and most opioid dependent individuals are young and living with parents who were very willing to monitor adherence. But even under these conditions, only 40-44% of patients treated with oral naltrexone remained in treatment for 6 months without relapsing [Krupitsky et al, 2004, 2006].

The National Institute on Drug Abuse supported efforts to develop sustained release naltrexone and address the adherence problem as early as the 1970's. Similar efforts occurred in Russia and they led to approval of a sustained release implant (Prodetoxon®) that blocks opioid effects for 2-3 months. Then in 2006 the FDA approved sustained release injectable naltrexone (Vivitrol®) for preventing relapse to alcohol dependence, and it was then approved for preventing relapse to opioid dependence in 2010 based on a study done by Krupitsky et al [2011].

Associated with these developments was concern that naltrexone might blunt responses to pleasurable stimuli since endogenous opioids help regulate mood and naltrexone blocks their effects but studies by Krupitsky et al [2006], O'Brien at al., [2010] and Mysels et al [2011] did not support this concern. Here we present additional information on this topic in a secondary analysis of data on craving, depression, anxiety and anhedonia from a randomized, double-blind, double-dummy trial comparing outcomes from the extended release implant (Prodetoxon®), oral naltrexone, and placebo [Krupitsky et al, 2012]. Our clinical experience suggested that naltrexone does not increase negative affects, however we thought the question worth exploring since the number of subjects in this study was relatively large as was the testing battery, and we could examine the question using both oral

and extended release formulations, each with somewhat different pharmacokinetics and pharmacodynamics.

METHODS

Study Sites and Participants

The trial was conducted at St. Petersburg Pavlov State Medical University and the Leningrad Regional Addiction Treatment Center. Institutional review boards at Pavlov and the University of Pennsylvania approved the study and written informed consent in Russian was obtained from each participant before enrollment. Most patients were recruited during detoxification on the inpatient units at the Leningrad Addiction Treatment Center and the St. Petersburg City Addiction Hospital, and a few were enrolled after completing outpatient detoxification.

Design

The parent study was a double blind, double dummy 24-week trial in which 306 individuals meeting DSM-IV criteria for opioid dependence were randomized to biweekly drug counseling and one of three treatment conditions of 102 patients each: 1) 1000 mg naltrexone implant every 8 weeks and oral naltrexone placebo; 2) placebo implant and daily 50 mg oral naltrexone; or 3) placebo implant and placebo oral.

Interventions

Medications

Naltrexone implant (Prodetoxon®) and placebo: The implant contains 1,000 mg of naltrexone embedded in a magnesium stearate matrix that has a small dose of triamcinolone to prevent inflammation. It is inserted under the skin of the abdominal wall to a depth of approximately 3-4 cm through a 1-2 cm incision made with a sterile, pre-packaged disposable syringe. Plasma levels over days 30-60 after implantation are 20 ng/ml for naltrexone and 60 ng/ml for 6ß-naltrexol, its active metabolite (Kukes et al., 2006). It blocks opioids for 2 or more months and is biodegradable, thus does not require removal (Kukes et al., 2006). Plasma levels beyond 60 days have not been measured but clinical experience suggests they are sufficient to block opioids up to 3 months. Fidelity Capital, the manufacturer of Prodetoxon®, provided the implants at reduced cost along with visually identical placebo. The placebo implant is made of the same materials but had no naltrexone.

Oral Naltrexone and placebo: The Zambon Group provided 50 mg naltrexone tablets (Antaxone®) at reduced cost. Pavlov pharmacy staff made visually identical oral naltrexone and placebo capsules containing a 50 mg riboflavin marker to monitor adherence. Studies of 50 mg tablets have shown plasma naltrexone levels peaking in 1-3 hours at 10-20 ng/ml and declining to approximately 0.5-1 ng/ml at 24 hours with a half-life of 4 hours; 6ß-naltrexol plasma levels reached about 8 times the peak naltrexone concentration and declined with a half-life of approximately 14 hours (Vereby et al. 1976; Mason et al. 2002). Blinding procedures are described in the primary outcome paper (Krupitsky et al, 2012).

Psychosocial: Individual Drug Counseling (IDC)—Counseling was adapted for treatment of opioid dependence from procedures that were used in the NIDA cocaine/psychotherapy study and are described in a manual that is available at (http://www.INda.INh.gov/TXManuals/IDCA/IDCA1.html). Modifications involved de-emphasizing self-help groups because they are not widely used in Russia, emphasizing adherence to medication and counseling, and dealing with persistent opioid withdrawal.

Measures

Medical and psychiatric examinations to rule out patients that were ineligible for the study were done at baseline, as were measures of drug use and overall adjustment (Krupitsky et al, 2012). Measures relevant to findings presented in this paper were the visual analog scale of heroin craving, Beck Depression Inventory (Beck et al., 1961), Spielberger State-Trait Anxiety Test (Spielberger, Anton & Bedell, 1976), and the Ferguson Anhedonia Scale (Ferguson et al., 2006). The first three measures were done at baseline and biweekly during the first 3 months and at 6 months; the Chapman Scale of Physical and Social Anhedonia (Chapman et al., 1976) was done at baseline and at 1, 2, 3 and 6 months. We did not attempt to measure craving, depression, anxiety, or anhedonia among patients who were known to have relapsed because these symptoms are typically unstable in the context of active drug use. Patients were reimbursed with the ruble equivalent of $10 for each study visit, potentially totaling $120 if a patient kept all study appointments.

Analyses

Data were double entered and checked for errors and the Statistical Package for the Social Sciences (version 17) was used to analyze the data. All variables were tested for normal distribution using the Kolmogorov-Smirnov criteria, the Fridman Test, and the Wilcoxon test for post hoc analysis to analyze for non-normally distributed variables. Categorical variables were examined with Fisher exact tests using Monte-Carlo modeling for more than 2 groups. To compare differences between categorical dichotomous variables we analyzed odds ratios with 95% confidence intervals and survival analysis (Kaplan-Meier Survival Functions with Log Rank Mantel-Cox criteria for group comparison; Kaplan & Meier, 1958) to compare retention in the three groups. Continuous data were examined by mixed model analysis of variance (Mixed ANOVA) that consisted of treatment groups and time as independent variables, and retention, relapse, and psychometric data as dependent variables. Tukey or Bonferroni tests were used for between-groups post hoc comparisons. Changes in Ferguson anhedonia scores were analyzed with the Fridman Test as well as the Wilcoxon test due to the ordinal nature of the data. Here we present analyses of psychometric findings for all participants that had data at each timepoint (visit) without imputing missing data since in this project, missing data cannot be accepted as Missing at Random or Completely at Random since relapse was the main cause of missed visits and not a random event. Tests were considered significant at $p<0.05$.

Results

Recruitment, Demographics and Outcomes—Patients were recruited from 2006 to 2008; 358 patients were asked if they were interested, 309 gave informed consent and 306

met study entrance criteria, completed baseline assessments and were randomized to one of the three groups resulting in 102/group. Mean age was 28.2±4.2 years (M±SD; 17- 40); average years dependent on heroin was 8.0±3.9 (M±SD); and use of alcohol and other drugs was minimal. There were no significant between group differences at baseline.

Treatment retention without relapsing, opiate urine test results, outcomes according to the Addiction Severity Index, and HIV risk behaviors all favored the implant group; details are in the primary outcome paper (Krupitsky et al, 2012).

Craving, Depression, Anxiety, Anhedonia—Craving was significantly reduced from 3-3.5 on a 10-point scale at baseline to 0.5-1.1 at six months among patients who remained in treatment and did not relapse, with no differences between groups. Overall levels of depression, anxiety, and anhedonia were moderately elevated at baseline with no between-group differences and gradually decreased to levels that were at or near normal within the first 1-2 months among those who remained in treatment and did not relapse, again with no differences between groups (Table 2).

To explore the possibility that worsening affects contributed to dropout we compared craving, depression, anxiety and anhedonia in the last measure obtained before the patient stopped study medication with the same measures for those that continued on medication. The only significant difference was in anxiety at week 2 between those who dropped out and those who remained in treatment, but that effect was small (46.2 vs 49.8; 47.3 vs 51.3), similar in direction to changes in the placebo group andfound at week 2 butno other follow-up points regardless of medication group (Table 3).

Discussion

As in two previous studies of oral naltrexone (Krupitsky et al 2004; 2006), but unlike the study of extended release injectable naltrexone (Krupitsky et al, 2011), opioid craving was not reduced. We cannot explain these differences but they might reflect the way craving was measured. In the study reported here and in our past oral naltrexone studies patients were asked to rate the intensity of craving for opiates “here and now” while in the extended release injectable naltrexone study the question was phrased “over the past week”. Differences in pharmacokinetics between injectable, implantable, and oral naltrexone, or the higher proportion of placebo patients with followup data in the extended release injectable study could also play a role (Krupitsky et al, 2011).

Most importantly, we did not find evidence that oral or implantable naltrexone increased craving, depression, anxiety or anhedonia among patients that continued in treatment and did not relapse, nor did we find much evidence of such problems when comparing the last measures obtained from patients that stopped taking study medication with the measures taken at the same point in time on those that continued on study medication. Though these findings do not prove that naltrexone never increases anxiety, depression and the other affects that were measured in this study, the relatively large sample size and placebo control indicate that if they occur, they are uncommon, consistent with the results of O'Brien et al (2010) who found no effect of long acting injectable naltrexone on hedonic response in alcohol dependent subjects.

In summary, these findings provide no support for the concern that naltrexone increases negative affects in patients being treated with it for opioid dependence. In fact the opposite appears to be true though not specific to the pharmacology of naltrexone, rather to its ability to facilitate remission. Having said this, it is important to keep in mind that regardless of treatment response, persons with opioid dependence have increased rates of depression as well as suicidal ideation and behavior, anxiety and other problems and need to be monitored and treated regardless of treatment modality.

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Table 1

Demographics and Clinical Characteristics

Medication group		NI+OP	PI+ON	PI+OP	All
No. Patients		102	102	102	306
Age (years) (M±SE)		28.0±0.40	27.9±0.39	28.7±0.45	28.2±0.24
Sex	Male n (%)	74(72.5%)	74(72.5%)	74(72.5%)	226(72.5%)
	Female n (%)	28(27.5%)	28(27.5%)	28(27.5%)	84(27.5%)
Duration of heroin abuse (years) (M±SE)		7.8±0.38	7.9±0.41	8.3±0.39	8.0±0.23
Average daily dose of heroin (mg) (M±SE)		1.1±0.07	0.9±0.08	0.9±0.07	1.0±0.04
Use of amphetamines n (%)		12(11.8%)	6(5.9%)	18(17.6%)	26(12%)
Use of cocaine n (%)		0(0%)	0(0%)	0(0%)	0(0%)
Use marijuana n (%)		35(34.3%)	22(21.6%)	25(24.5%)	82(27%)
Use of sedatives (benzodiazepines) n (%)		15(14.7%)	10(9.8%)	9(8.8%)	34(11%)
Use of alcohol (grams of ethanol per day)		10.2±1.69	9.0±1.72	9.6±1.58	9.6±0.96
Number of previous treatments (M±SE)		4.9±0.41	4.3±0.37	3.8±0.31	4.3±0.21
Employment n (%)		47(46.1%)	42(41.2%)	51(50.0%)	140(46%)
HIV positive n (%)		44(43.0%)	53(52.0%)	47(46.5%)	144(47%)
Hepatitis B n (%)		18(17.8%)	16(16.0%)	13(13.0%)	47(15%)
Hepatitis C n (%)		98(96.1%)	98(96.0%)	96(95.1%)	293(96%)
RAB drug risk, score		8.0±0.47	8.1±0.44	8.7±0.49	8.2±0.27
GAF, score		64.7±0.81	62.8±0.72	62.5±0.90	63.3±0.47
ASI medical problems (M±SE)		0.13±0.23	0.07±0.11	0.09±0.14	0.10±0.12
ASI work problems (M±SE)		0.68±0.28	0.72±0.26	0.76±0.26	0.73±0.20
ASI alcohol use problems (M±SE)		0.11±0.12	0.08±0.09	0.10±0.09	0.10±0.06
ASI drug use problems (M±SE)		0.29±0.06	0.29±0.06	0.29±0.09	0.29±0.04
ASI law problems (M±SE)		0.11±0.21	0.07±0.11	0.10±0.15	0.09±0.09
ASI family problems (M±SE)		0.34±0.30	0.31±0.19	0.30±0.19	0.32±0.13
ASI psychiatric problems (M±SE)		0.15±0.18	0.19±0.20	0.18±0.21	0.17±0.11

Note: There is no significant between group differences.

RAB – Risk Assessment Battery;

GAF – Global Assessment of Functioning Scale;

ASI – Addiction Severity Index

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Table 2

Craving, Depression, Anxiety, and Anhedonia

Number of patients	**NI+OP**	102	96	83	76	54	
	PI+ON	102	65	46	32	16	
	PI+OP	102	50	32	28	11	
RATING SCALES	**Medication groups**	**Psychometric data (by weeks of medication)**					
		0	**4**	**8**	**12**	**24**	
Craving for opiates M±SEM	**NI+OP**	3.05±0.28	1.09±0.20 *	1.01±0.19 *	0.70±0.17 *	0.33±0.19 *	Mixed ANOVA Main Time effect $F_{4.750}$=44.71; P=<. 01
	PI+ON	3.30±0.28	1.25±0.28 *	0.50±0.13 *	1.07±0.37 *	0.29±0.11 *	
	PI+OP	3.18±0.28	1.15±0.25 *	0.70±0.21 *	0.53±0.20 *	1.09±0.84 *	
Beck depression scale M±SEM	**NI+OP**	18.76±0.91	8.91±0.72 *	7.03±0.80 *	5.28±0.73 *	2.80±0.49 *	Mixed ANOVA Main Time effect $F_{4.750}$=161.80; P=<. 01
	PI+ON	19.92±0.80	9.62±1.06 *	6.45±1.16 *	7.62±1.45 *	6.11±2.03 *	
	PI+OP	20.76±0.83	8.50±1.05 *	6.32±1.33 *	5.00±1.17 *	1.50±0.73 *	
Spielberger state anxiety scale M±SEM	**NI+OP**	46.4±1.06	40.9±1.45 *	38.7±1.32 *	36.1±1.17 *	34.4±1.34 *	Mixed ANOVA Main Time effect $F_{4.750}$=30.82; P=<. 01
	PI+ON	47.0±0.90	42.2±1.61 *	39.7±1.64 *	40.6±1.87 *	38.8±2.14 *	
	PI+OP	48.6±1.00	40.9±1.64 *	36.5±1.74 *	38.6±1.91 *	36.6±3.82 *	
Spielberger trait anxiety scale M±SEM	**NI+OP**	48.0±0.99	43.1±1.03 *	40.1±0.94 *	39.4±0.89 *	37.7±0.93 *	Mixed ANOVA Main Time effect $F_{4.750}$=31.88; P=<. 01
	PI+ON	48.2±0.91	44.3±1.46 *	38.6±1.30 *	41.4±1.52 *	40.3±1.47 *	
	PI+OP	48.5±0.87	41.5±1.27 *	41.3±1.79 *	39.0±1.73 *	39.2±2.27 *	
Lack of Pleasure (Ferguson Anhedonia Scale) M±SEM Me (min-max)	**NI+OP**	1.00±0.10 1 (0-4)	0.60±0.10 0 (0-3) +	0.23±0.47 0 (0-1) +	0.13±0.05 0 (0-2) +	0.07±0.45 0 (0-2) +	Fridman Test P=<. 01
	PI+ON	1.12±0.10 1 (0-4)	0.67±0.14 0 (0-3) +	0.35±0.10 0 (0-2) +	0.28±0.10 0 (0-2) +	0.06±0.56 0 (0-2) +	Fridman Test P=<. 01
	PI+OP	1.20±0.10 1 (0-4)	0.48±0.11 0 (0-4) +	0.19±0.86 0 (0-2) +	0.17±0.08 0 (0-1) +	0 0 (0-0) +	Fridman Test P=<. 01
Lack of Interest (Ferguson Anhedonia Scale) M±SEM Me (min-max)	**NI+OP**	1.15±0.96 1 (0-4)	0.56±0.10 0 (0-3) +	0.33±0.59 0 (0-2) +	0.20±0.59 0 (0-2) +	0.06±0.41 0 (0-2) +	Fridman Test P=0.06

	PI+ON	1.24±0.10 1 (0-4)	0.70±0.13 0 (0-4) +	0.41±0.96 0 (0-3) +	0.33±0.98 0 (0-2) +	0.06±0.56 0 (0-1) +	Fridman Test P=0.04
	PI+OP	1.43±0.117 1 (0-4)	0.39±0.081 0 (0-3) +	0.23±0.089 0 (0-2) +	0.26±0.113 0 (0-2) +	0 0 (0-0) +	Fridman Test P=<. 0001
Physical Anhedonia (Chapman scale) M±SEM	**NI+OP**	28.9±1.39			26.3±1.51 *	26.7±1.66 *	Mixed ANOVA Main Time effect $F_{2.210}$=30.13; P=<. 01
	PI+ON	27.7±1.34			21.8±2.13 *	19.6±1.96 *	
	PI+OP	26.4±1.26			23.3±2.92 *	14.6±2.96 *	
Social Anhedonia (Chapman scale) M±SEM	**NI+OP**	20.4±0.90			18.4±0.96 *	18.6±1.15 *	Mixed ANOVA Main Time effect $F_{2.210}$=14.03; P=<. 01
	PI+ON	19.4±0.95			17.2±1.63 *	15.8±2.93 *	
	PI+OP	18.1±0.86			16.1±1.79 *	14.3±2.44 *	

Notes: 1.Statistical significance of differences between psychometrics at intake (0 month) and further assessments (Mixed ANOVA Main Time effect. Tukey test for post hoc comparisons):

Main Group effects and interaction Time*Group effects for all variables are non-significant.

2. Statistical significance of differences between psychometrics at intake (0 month) and further assessments (Fridman Test and Wilcoxon Signed Ranks Test for post hoc comparisons):

Mann–Whitney U test Between Group comparisons at all time points are non-significant.

3. The means are the means for all patients with data at a given time point.

* p<0.01.

+ p<0.05.

Comparisons: Continuing Treatment vs. Last Measure Before Dropout

Group		Endpoint				ANOVA
		Continued Treatment		Before Dropout		
		N	Mean±Std. Error	N	Mean±Std. Error	
Craving for opiates						
2 weeks	PI+OP	64	3.2±0.36	38	3.1±0.46	Main group effect F2, 300=1.374; P=0.255 Main endpoint effect F1, 300=0.144; P=0.704 group*endpoint interaction F2, 300=2.305; P=0.102
	PI+ON	79	2.9±0.32	23	4.5±0.60	
	NI+OP	97	3.1±0.29	5	2.2±1.28	
4 weeks	PI+OP	50	1.4±0.31	14	1.9±0.63	Main group effect F2, 234=0.483; P=0.617 Main endpoint effect F1, 234=0.016; P=0.899 group*endpoint interaction F2, 234=0.385; P=0.680
	PI+ON	65	1.0±0.27	14	1.6±0.70	
	NI+OP	96	1.4±0.22	1	0.0±2.10	
8 weeks	PI+OP	30	0.5±0.26	2	0.3±0.63	Main group effect F2, 155=3.014; P=0.052 Main endpoint effect F1, 155=0.109; P=0.741 group*endpoint interaction F2, 155=0.944; P=0.391
	PI+ON	40	0.7±0.22	6	0.1±0.45	
	NI+OP	79	1.1±0.17	4	1.5±0.58	
12 weeks	PI+OP	28	0.7±0.32	2	0.0±1.49	Main group effect F2, 143 =0.013; P=0.987 Main endpoint effect F1, 143 =1.032; P=0.312 group*endpoint interaction F2, 143 =0.009; P=0.990
	PI+ON	32	0.7±0.30	8	0.2±0.61	
	NI+OP	76	0.7±0.21	3	0.0±1.05	
Beck Depression						
2 weeks	PI+OP	64	19.5±1.07	38	23.0±1.39	Main group effect F2, 300=0.199; P=0.819 Main endpoint effect F1, 300=3.464; P=0.064 group*endpoint interaction F2, 300=0.066; P=0.07
	PI+ON	79	19.3±0.96	23	21.9±1.79	
	NI+OP	97	18.6±0.87	5	21.4±3.83	
4 weeks	PI+OP	50	10.5±1.27	14	14.3±2.60	Main group effect F2, 234=0.353; P=0.703 Main endpoint effect F1, 234=0.152; P=0.697 group*endpoint interaction F2, 234=1.523; P=0.220
	PI+ON	65	12.2±1.10	14	9.0±2.87	
	NI+OP	96	13.3±0.92	1	9.0±8.62	
8 weeks	PI+OP	30	7.3±1.45	2	6.0±3.48	Main group effect F2, 155=0.801; P=0.450 Main endpoint effect F1, 155=0.059; P=0.809 group*endpoint interaction F2, 155=0.762; P=0.469
	PI+ON	40	8.7±1.22	6	6.0±2.46	
	NI+OP	79	8.3±0.91	4	10.8±3.18	
12 weeks	PI+OP	28	4.7±1.55	2	21.0±7.10	Main group effect F2, 143=1.028; P=0.361 Main endpoint effect F1, 143=4.577; P=0.035 group*endpoint interaction F2, 143=2.014; P=0.139
	PI+ON	32	7.2±1.42	8	7.5±2.90	

Group		Endpoint				ANOVA
		Continued Treatment		Before Dropout		
		N	Mean±Std. Error	N	Mean±Std. Error	
	NI+OP	76	5.4±1.00	3	9.0±5.02	
Spielberger State Anxiety						
2 weeks	PI+OP	64	47.6±1.24	38	50.2±1.61	Main group effect F2, 300=0.264; P=0.768 Main endpoint effect F1, 300=5.906; **P=0.016** group*endpoint interaction F2, 300=0.433; P=0.649
	PI+ON	79	46.2±1.12	23	49.8±2.07	
	NI+OP	97	46.0±1.01	5	53.2±4.44	
4 weeks	PI+OP	50	41.2±1.73	14	45.6±3.54	Main group effect F2, 234=2.182; P=0.115 Main endpoint effect F1, 234=2.699; P=0.102 group*endpoint interaction F2, 234=2.390; P=0.094
	PI+ON	65	42.6±1.51	14	38.9±3.92	
	NI+OP	96	43.1±1.25	1	64.0±11.76	
8 weeks	PI+OP	30	38.7±2.32	2	38.2±5.58	Main group effect F2, 155=1.070; P=0.345 Main endpoint effect F1, 155=0.004; P=0.951 group*endpoint interaction F2, 155=0.378; P=0.686
	PI+ON	40	39.8±1.95	6	36.8±3.94	
	NI+OP	79	41.5±1.46	4	44.5±5.09	
12 weeks	PI+OP	28	37.0±2.39	2	42.0±10.96	Main group effect F2, 143=0.057; P=0.945 Main endpoint effect F1, 143=0.292; P=0.590 group*endpoint interaction F2, 143=0.586; P=0.559
	PI+ON	32	43.1±2.24	8	40.0±4.47	
	NI+OP	76	37.9±1.55	3	44.0±7.75	
Spielberger Trait Anxiety						
2 weeks	PI+OP	64	47.3±1.16	38	50.5±1.51	Main group effect F2, 300=0.092; P=0.912 Main endpoint effect F1, 300=4.694; **P=0.031** group*endpoint interaction F2, 300=0.037; P=0.963
	PI+ON	79	47.3±1.04	23	51.3±1.94	
	NI+OP	97	47.8±0.94	5	51.8±4.15	
4 weeks	PI+OP	50	42.9±1.49	14	44.2±3.04	Main group effect F2, 234=0.189; P=0.828 Main endpoint effect F1, 234=0.340; P=0.560 group*endpoint interaction F2, 234=0.424; P=0.655
	PI+ON	65	43.0±1.29	14	43.7±3.36	
	NI+OP	96	44.5±1.08	1	36.0±10.08	
8 weeks	PI+OP	30	40.4±1.90	2	41.6±4.57	Main group effect F2, 155=1.548; P=0.216 Main endpoint effect F1, 155=0.003; P=0.960 group*endpoint interaction F2, 155=1.228; P=0.296
	PI+ON	40	41.5±1.60	6	36.5±3.23	
	NI+OP	79	42.2±1.20	4	45.7±4.17	
12 weeks	PI+OP	28	39.9±2.22	2	59.0±10.16	Main group effect F2, 143=1.508; P=0.226 Main endpoint effect F1, 143=1.498; P=0.224 group*endpoint interaction F2, 143=1.825; P=0.167
	PI+ON	32	41.3±2.07	8	38.7±4.15	
	NI+OP	76	39.4±1.44	3	39.5±7.18	

Group		Endpoint				ANOVA
		Continued Treatment		Before Dropout		
		N	Mean±Std. Error	N	Mean±Std. Error	
Ferguson Anhedonia (Lack of Pleasure)						
2 weeks	PI+OP	64	1.4±0.14	38	1.4±0.18	Main group effect F2, 300=1.262; P=0.284 Main endpoint effect F1, 300=0.005; P=0.944 group*endpoint interaction F2, 300=0.555; P=0.575 Main endpoint effect (Mann-Whitney U) P=0.931
	PI+ON	79	1.3±0.12	23	1.0±0.23	
	NI+OP	97	1.1±0.11	5	1.4±0.48	
4 weeks	PI+OP	50	0.5±0.17	14	0.9±0.34	Main group effect F2, 234=0.204; P=0.816 Main endpoint effect F1, 234=0.548; P=0.460 group*endpoint interaction F2, 234=1.429; P=0.242 Main endpoint effect (Mann-Whitney U) P=0.858
	PI+ON	65	0.8±0.15	14	0.3±0.38	
	NI+OP	96	0.9±0.12	1	0.0±1.14	
8 weeks	PI+OP	30	0.3±0.16	2	0.6±0.38	Main group effect F2, 155=2.292; P=0.104 Main endpoint effect F1, 155=0.931; P=0.336 group*endpoint interaction F2, 155=2.207; P=0.113 Main endpoint effect (Mann-Whitney U) P=0.812
	PI+ON	40	0.5±0.13	6	0.2±0.27	
	NI+OP	79	0.5±0.10	4	1.2±0.35	
12 weeks	PI+OP	28	0.3±0.12	2	1.0±0.54	Main group effect F2, 143=2.270; P=0.109 Main endpoint effect F1, 143=1.457; P=0.230 group*endpoint interaction F2, 143=0.887; P=0.415 Main endpoint effect (Mann-Whitney U) P=0.070
	PI+ON	32	0.4±0.11	8	0.7±0.22	
	NI+OP	76	0.1±0.08	3	0.0±0.39	
Ferguson Anhedonia (Lack of Interest)						
2 weeks	PI+OP	64	1.2±0.13	38	1.2±0.17	Main group effect F2, 300=0.237; P=0.789 Main endpoint effect F1, 300=0.055; P=0.944 group*endpoint interaction F2, 300=0.173; P=0.842 Main endpoint effect (Mann-Whitney U) P=0.792
	PI+ON	79	1.1±0.12	23	1.0±0.22	
	NI+OP	97	1.0±0.11	5	1.2±0.47	
4 weeks	PI+OP	50	0.6±0.16	14	0.8±0.32	Main group effect F2, 234=0.286; P=0.752 Main endpoint effect F1, 234=0.969; P=0.326 group*endpoint interaction F2, 234=1.468; P=0.233 Main endpoint effect (Mann-Whitney U) P=0.272
	PI+ON	65	0.8±0.14	14	0.2±0.36	
	NI+OP	96	0.9±0.11	1	0.0±1.07	
8 weeks	PI+OP	30	0.2±0.15	2	0.6±0.37	Main group effect F2, 155=1.504; P=0.225 Main endpoint effect F1, 155=2.123; P=0.147 group*endpoint interaction F2, 155=1.797; P=0.169 Main endpoint effect (Mann-Whitney U) P=0.502
	PI+ON	40	0.6±0.13	6	0.4±0.26	
	NI+OP	79	0.5±0.10	4	1.2±0.34	
12 weeks	PI+OP	28	0.2±0.14	2	1.0±0.60	Main group effect F2, 143=1.954; P=0.147 Main endpoint effect F1, 143=1.775; P=0.186 group*endpoint interaction F2, 143=1.161; P=0.317 Main endpoint effect (Mann-Whitney U) P=0.070
	PI+ON	32	0.4±0.12	8	0.8±0.25	
	NI+OP	76	0.2±0.09	3	0.0±0.43	

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