Naltrexone for impulse control disorders in Parkinson disease

A placebo-controlled study

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ABSTRACT

Objective: Impulse control disorders (ICDs) in Parkinson disease (PD) are common and can be difficult to manage. The objective of this study was to determine the efficacy and tolerability of naltrexone, an opioid antagonist, for the treatment of ICDs in PD.

Methods: Patients with PD (n = 50) and an ICD were enrolled in an 8-week, randomized (1:1), double-blind, placebo-controlled study of naltrexone 50–100 mg/d (flexible dosing). The primary outcome measure was response based on the Clinical Global Impression–Change score, and the secondary outcome measure was change in symptom severity using the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS) ICD score.

Results: Forty-five patients (90%) completed the study. The Clinical Global Impression–Change response rate difference favoring naltrexone in completers was 19.8% (95% confidence interval [CI] −8.7% to 44.2%). While this difference was not significant (odds ratio = 1.6, 95% CI 0.5–5.2, Wald χ^2 [*df*] = 0.5 [1], $p = 0.5$), naltrexone treatment led to a significantly greater decrease in QUIP-RS ICD score over time compared with placebo (regression coefficient for interaction term in linear mixed-effects model = −7.37, F[*df*] = 4.3 [1, 49], $p = 0.04$). The estimated changes in QUIP-RS ICD scores from baseline to week 8 were 14.9 points (95% CI 9.9–19.9) for naltrexone and 7.5 points (95% CI 2.5–12.6) for placebo.

Conclusions: Naltrexone treatment was not efficacious for the treatment of ICDs in PD using a global assessment of response, but findings using a PD-specific ICD rating scale support further evaluation of opioid antagonists for the treatment of ICD symptoms in PD.

Classification of evidence: This study provides Class I evidence that in patients with PD and an ICD, naltrexone does not significantly increase the probability of achieving response. However, the study lacked the precision to exclude an important difference in response rates. *Neurology*® 2014;83:826–833

GLOSSARY

CGI-C = Clinical Global Impression–Change; **CI** = confidence interval; **DA** = dopamine agonist; **DBS** = deep brain stimulation; ***df*** = degrees of freedom; ***DSM-IV-TR*** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision*; **GEE** = generalized estimating equation; **HA** = harm avoidance; **ICD** = impulse control disorder; **NS** = novelty seeking; **PD** = Parkinson disease; **PG** = pathological gambling; **QUIP-RS** = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale; **RD** = reward dependence; **TPQ** = Tridimensional Personality Questionnaire; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Impulse control disorders (ICDs; compulsive gambling, buying, sexual behavior, and eating) occur relatively frequently in Parkinson disease (PD).[1] In a large multisite observational study, at least one ICD was identified in 14% of patients with PD.[2] ICDs were more common in patients taking a dopamine agonist (DA), which has emerged as the strongest potential risk factor for ICDs. ICD behaviors range widely in severity but can lead to devastating consequences, including financial ruin, divorce, loss of employment, and increased health risks. In general, ICDs are associated with greater functional impairment,[3] decreased quality of life,[4] and increased caregiver burden.[5]

ICD behaviors can resolve after discontinuing DA treatment,[6] but many patients do not tolerate this intervention, and a DA withdrawal syndrome has been described.[7] Deep brain

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stimulation (DBS) surgery is a possible treatment option, but the relationship between DBS surgery and ICDs is complex, and new-onset ICD symptoms post-DBS surgery have been reported.[8] A range of psychiatric treatments (e.g., antidepressants, antipsychotics, and anticonvulsants) have been used for ICDs in PD, but experimental evidence supporting their use in PD is lacking. A small placebo-controlled study reported benefit for amantadine as a treatment for pathological gambling (PG),[9] but amantadine use has also been associated with ICDs in PD.[10]

Naltrexone, a competitive, nonselective opioid receptor antagonist, is efficacious in the treatment of alcohol[11] and opioid[12] dependence, and is US Food and Drug Administration-approved for the treatment of alcohol dependence at a dosage of 50 mg/d. A controlled naltrexone study (up to 250 mg/d) demonstrated efficacy for PG in the general population,[13] and case reports at doses of 100–150 mg/d suggest its benefit for other ICDs.[14–16] In addition, the tolerability of naltrexone in patients with PD was good when tested for its antiparkinsonian effects at 100 mg/d.[17]

The primary objective for this study was to assess the efficacy of naltrexone for the treatment of ICDs in PD. We hypothesized that naltrexone would lead to global clinical improvement across the range of ICDs that are reported to occur in PD.

METHODS

Participants. Fifty participants aged 18 to 85 years with a diagnosis of idiopathic PD[18] and compulsive gambling, buying, sexual behaviors, or eating were enrolled in the study. ICD symptoms had to have begun after (1) PD onset and (2) initiation of DA treatment. The following diagnostic criteria for ICDs were applied[1]: *DSM-IV-TR* criteria for pathological or problem gambling[19,20]; McElroy criteria for compulsive buying[21]; Voon criteria for compulsive sexual behavior[22]; and modified *DSM-IV-TR* proposed criteria for binge-eating disorder[19] (to include not only discrete binge-eating episodes, but also generalized overeating in excess of previous eating behaviors), as used previously in our ICD research.[23]

Participants were required to have been taking their current DA (ropinirole or pramipexole in all cases) for >6 months and on a stable dose for >1 month. Exclusion criteria were a Montreal Cognitive Assessment[24] score <20 (to exclude patients likely with dementia), active suicide ideation, history of DBS within the past year or onset of ICD symptoms temporally related to DBS surgery, active liver disease, alcohol or opiate dependence, overlapping psychiatric diagnoses (i.e., bipolar disorder and dopamine dysregulation syndrome), and use of opioids for pain management. Patients were instructed not to change their PD management (medications or DBS settings) during the course of the study (4 participants made slight modifications to their DA treatment during the course of the study, 3 in the naltrexone group and one in the placebo group; no patients changed their DBS settings just before or during the course of the study).

Standard protocol approvals, registrations, and patient consents. Approval from the institutional ethical standards committee on human experimentation was obtained before study initiation, and written informed consent for research was obtained from all study participants. Clinical trial registration: ClinicalTrials.gov, identifier NCT01052831.

Study design. The study was a single-site, 8-week, 1:1 randomized, double-blind, parallel, placebo-controlled, flexible dose (50–100 mg/d) trial. Participants were randomly assigned to treatment groups using computer-generated variable block sizes (2 or 4 participants per block), with numbers sealed in opaque envelopes. Participants were evaluated at baseline, week 2, week 4, week 6, and week 8 (end-of-study visit). The baseline, week 4, and week 8 visits were in-person, and the week 2 and week 6 visits were conducted by telephone. For the first 4 weeks, all participants were administered naltrexone at 50 mg/d (or matching placebo). Participants not in response (a score of 1 or 2 on the Clinical Global Impression–Change [CGI-C]) at week 4 were increased to 100 mg/d naltrexone (or matching placebo) for the final 4 weeks. At study completion or termination, all study participants were offered routine clinical care (with D.W.), including the option to take naltrexone.

Study outcomes. An unstructured, clinician-completed (D.W.) CGI-C[25] was chosen as the primary outcome measure of change in ICD symptoms (range of 1–7, 1 indicating very much improved, 7 indicating very much worse, compared with baseline) because there was no single PD ICD rating scale when the study was conceptualized. For this study, CGI-C scores were analyzed as a dichotomous variable (score of 1 or 2 was used to indicate response, all other scores indicated nonresponse—as often done in psychiatric clinical trials[26,27]) for both intent-to-treat analysis and study completers analysis.

Just before study initiation, the patient-completed Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS) was developed[23] for use in clinical trials and added as a secondary outcome measure for assessment of change in severity of ICD symptoms, to be completed at baseline and end of study only. For the QUIP-RS, scores for each compulsive behavior range from 0 to 16, with a higher score indicating greater severity (frequency) of symptoms. Given that ICD symptoms are frequently comorbid in patients with PD, total QUIP-RS ICD scores (range from 0 to 64) were used to compare overall severity of ICD symptoms. In the validation study, the mean (SD) QUIP-RS ICD score (SD) was 22.5 (11.0) in patients with PD and an ICD and 5.6 (8.0) in patients without an ICD.

Other outcome measures collected included the 15-item Geriatric Depression Scale and the Beck Hopelessness Scale. Although not designed for use in clinical trials, the Barratt Impulsivity Scale (total score and 3 subscales: attentional, motor, and nonplanning) and the Tridimensional Personality Questionnaire (TPQ; 3 subscales: reward dependence [RD], harm avoidance [HA], and novelty seeking [NS]) were included as exploratory measures because of their association with ICDs in PD.[3]

Motor severity was assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) motor score (Part III) and Hoehn and Yahr stage,[28] and levodopa and DA dosages were converted to levodopa equivalent daily dosages.[29] Adverse events were recorded using a version of the Treatment Emergent Symptoms Scale,[25] modified for use in neuropsychiatric studies in PD.[30]

Statistical methods. Primary analyses were conducted using the intent-to-treat population (i.e., all 50 randomized participants included). Baseline characteristics were compared with χ^2, *t* test, or nonparametric tests. For the change in response status over time, a generalized estimating equation (GEE)[31] was used, with response status (binary outcome) on CGI-C score as the dependent variable, group and visit week (continuous variable) as the primary independent variables, and baseline QUIP-RS ICD score and variables that demonstrated between-group discrepancy at baseline as covariates (i.e., history of DBS and comorbid ICDs). The GEE approach accounts for correlations among repeated measures of CGI-C scores and permits estimation of between-group difference without necessitating last observation carried forward or exclusion of participants with missing data. A Fisher exact test was used for comparing response status in the completers analysis. The association between response status and percentage change in QUIP-RS ICD score among completers was examined via a *t* test.

For the change in total QUIP-RS ICD score over time, a linear mixed-effects model[32] was used, with QUIP-RS ICD score as the dependent variable and group, week 8 (binary indicator indicating end of study), and interaction between group and week 8 as primary independent variables, with other covariates included as for the GEE model. The above independent variables and covariates were fixed effects in the model. The interaction term "week 8 × treatment group" represents the effect of the treatment on change in QUIP-RS ICD scores (i.e., between-group difference of change) at the end of study. The mixed-effects model considers within-subject correlations from repeated measurements of QUIP-RS ICD scores in the same subjects and allows estimation of between-group difference without necessitating last observation carried forward or exclusion of participants with missing data. Because QUIP-RS ICD scores were only evaluated at 2 time points, we report change of QUIP-RS at the end of study. We first examined a model with the fixed effects listed above and random effects including a random intercept and the regression coefficient for week 8, but this random-effects model did not fit the data because of the lack of model convergence. We thus relied on a model with the same fixed effects listed above and a simpler correlation structure: within-subject compound symmetry correlation structure without random effects. This model does not assume that the group difference is the same across time points because of the inclusion of an interaction between group and week 8. Linear mixed-effects models were also applied to analyze other outcome measures. The regression to the mean effects on the change in QUIP-RS was estimated using the method described by Davis.[33]

Using the response status based on the CGI-C as the primary outcome measure, we estimated a 75% vs 25% response rate in naltrexone- vs placebo-treated patients based on the results of a naltrexone study for PG in the general population.[13] A total sample size of 36 subjects was required to detect this difference in response rate with 80% power at the 0.05 significance level based on the 2-sided Fisher exact test. Allowing for a study discontinuation rate of approximately 20%, the minimum sample size was set at 46 participants.

Analyses were conducted with SPSS 20.0 (IBM Corp., Armonk, NY), and p value ≤ 0.05 was considered significant. All statistical tests were 2-sided.

RESULTS

Participant characteristics. Twenty-six participants were randomized to naltrexone and 24 to placebo. Forty-five patients (90%) completed the study (figure 1). Demographic and clinical information is listed in table 1. There were between-group differences in frequency of comorbid ICDs (50% in the naltrexone group vs 21% in the placebo group) and history of DBS (17% of placebo patients had undergone DBS surgery, compared with no patients in the naltrexone group), so these variables were entered as covariates in the mixed-effects models.

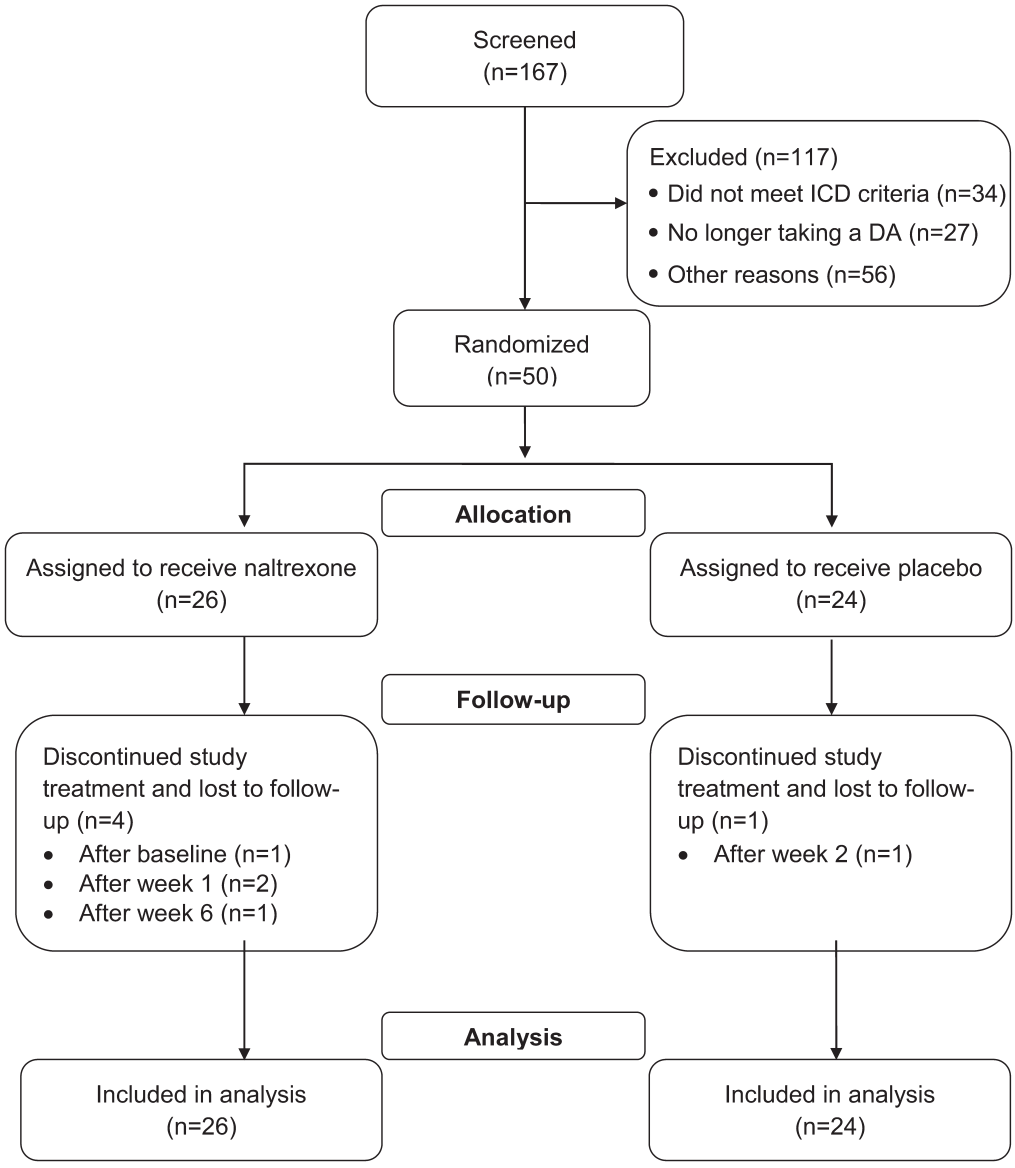
Primary outcome measure: CGI-C. In the GEE model, there was no between-group difference for response status over time using the CGI-C, with an estimated response rate at week 8 of 54.4% in the naltrexone group and 33.1% in the placebo group (odds ratio = 1.57, 95% confidence interval [CI] 0.47–5.23, Wald χ^2 [*df*] = 0.53 [1], $p = 0.47$). In this model, only visit week predicted response (Wald χ^2 [*df*] = 5.90 [1], $p = 0.02$).

Secondary outcome measure: QUIP-RS. In the linear mixed-effects model, naltrexone treatment led to a greater decrease in QUIP-RS ICD score over time compared with placebo (table 2). The estimated changes in QUIP-RS ICD scores from baseline to week 8 were as follows: 14.92 points (95% CI 9.89–19.96) in the naltrexone group and 7.55 points (95% CI 2.45–12.66) in the placebo group, with a between-group difference (controlling for the baseline QUIP-RS score and other covariates) of −7.37 points (95% CI −14.54 to −0.20, regression coefficient for interaction term = −7.37, F[*df*] = 4.26 [1, 49], $p = 0.04$). Other predictors of QUIP-RS ICD score were baseline QUIP-RS ICD score (regression coefficient = 0.81, F[*df*] = 317.46 [1, 46], $p < 0.001$) and week 8 (regression coefficient = −7.55, F[*df*] = 39.64 [1, 49], $p < 0.001$). The p value for the naltrexone treatment effect remained 0.04 when excluding the 4 patients who slightly modified their DA treatment during the course of the study.

Completers analyses. There were no significant differences between study completers (n = 45) and noncompleters (n = 5) in age, education, duration of PD, or baseline QUIP-RS ICD score (data not shown). For study completers, response rate based on the CGI-C score was 54.5% in the naltrexone group and 34.8% in the placebo group (Fisher exact test, $p = 0.23$). The response rate difference favoring naltrexone in completers was 19.8% (95% CI −8.7% to 44.2%). In this subset, the mean (SD) change in QUIP-RS ICD score over time was 15.27 (15.73) in naltrexone group vs 7.69 (8.84) in the placebo group (figure 2).

Measuring meaningfulness of response, the minimum clinically important difference (0.5 SD of change in QUIP-RS ICD score over time in study completers[34]) was ≥7 points, and 60% of naltrexone-treated completers met this criterion for improvement. Finally, the estimated regression to the mean effect in

Figure 1 CONSORT flowchart



CONSORT = Consolidated Standards of Reporting Trials; DA = dopamine agonist; ICD = impulse control disorder.

QUIP-RS was small (0.36 in the placebo group and 0.86 in the naltrexone group) relative to the mean change in both groups, indicating that the main source of the QUIP-RS change was not from the effect of regression to the mean. The between-group difference of regression to the mean effects was also small (0.50).

Other outcome measures. For participants who provided complete data on other outcome measures (n = 38), there was no effect of naltrexone treatment on change in the 15-item Geriatric Depression Scale ($p = 0.88$), Beck Hopelessness Scale ($p = 0.70$), total Barratt Impulsivity Scale ($p = 0.60$) or any Barratt Impulsivity Scale subscale (data not shown), or the TPQ-HA ($p = 0.27$) or TPQ-RD ($p = 0.86$) subscales. However, there was a significantly greater decrease in novelty-seeking traits (TPQ-NS score) over time in the naltrexone group compared with the placebo group, with a between-group difference (controlling for the baseline TPQ-NS score and other covariates) of −2.41 points (95% CI −4.75 to −0.08, regression coefficient for interaction term = −2.41, $F[df] = 4.39$ [1, 36], $p = 0.04$).

Motor outcomes. Using observed cases, UPDRS motor scores changed from a mean (SD) of 19.5 (9.5) to 18.1 (8.6) in the naltrexone group, and from 24.9 (10.7) to 21.8 (11.1) in the placebo group. There were no between-group differences for change in UPDRS motor score over time (regression coefficient for interaction term = −0.229, $F[df] = 0.003$ [1, 43], $p = 0.96$).

Adverse events. A total of 48 patients provided adverse event data. New-onset nausea possibly attributed to

Table 1 Participant clinical and demographic characteristics

Demographics	Total population	Naltrexone group	Placebo group	Statistic, χ^2 (*df*), *t* test (*df*), or nonparametric test, *p* value
Sex, % male	68.0	61.5	75.0	1.04 (1), $p = 0.31$
Race, % white	92.0	92.3	91.7	1.34 (2), $p = 0.51$
Ethnicity, % Hispanic	2.0	0.0	4.2	1.11 (1), $p = 0.29$
Marital status, % married	68.0	69.2	66.7	0.04 (2), $p = 0.98$
Age, y	61.2 (8.5)	61.3 (9.0)	61.0 (8.2)	−0.09 (48), $p = 0.93$
MoCA	27.2 (1.94)	26.9 (2.1)	27.58 (1.7)	1.21 (48), $p = 0.23$
Education, y	16.2 (3.2)	16.5 (3.2)	15.8 (3.2)	−0.82 (48), $p = 0.42$
Clinical				
Antidepressant, % yes	36.0	30.8	41.7	0.64 (1), $p = 0.42$
PD duration, y	8.4 (6.6)	7.35 (6.0)	9.50 (7.2)	1.16 (48), $p = 0.25$
DBS, % yes	8.0	0.0	16.7	4.71 (1), $p = 0.03$
Levodopa LEDD, mg/d	576.2 (407.5)	559.2 (410.7)	594.7 (411.9)	0.31 (48), $p = 0.76$
DA LEDD, mg/d	287.2 (237.9)	247.6 (130.9)	330.0 (313.4)	1.23 (48), $p = 0.23$
Total LEDD, mg/d	861.4 (473.4)	806.8 (454.4)	920.5 (496.0)	0.85 (48), $p = 0.40$
UPDRS motor score	22.1 (10.3)	19.5 (9.5)	24.9 (10.70)	1.90 (48), $p = 0.06$
Hoehn & Yahr stage	2.0 (2.0–2.5)	2.0 (2.0–2.5)	2.0 (2.0–3.0)	$p = 0.84$
ICD diagnosis				
Gambling, %	18.0	19.2	16.7	0.06 (1), $p = 0.81$
Sex, %	30.0	34.6	37.5	0.05 (1), $p = 0.83$
Buying, %	36.0	34.6	25.0	0.55 (1), $p = 0.46$
Eating, %	60.0	69.2	50.0	1.92 (1), $p = 0.17$
Multiple ICDs, %	36.0	50.0	20.8	4.61 (1), $p = 0.03$
Baseline QUIP-RS ICD score	32.8 (17.8)	35.4 (17.9)	30.0 (17.6)	−1.08 (48), $p = 0.29$

Abbreviations: DA = dopamine agonist; DBS = deep brain stimulation; *df* = degrees of freedom; ICD = impulse control disorder; LEDD = levodopa equivalent daily dosage; MoCA = Montreal Cognitive Assessment; PD = Parkinson disease; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale; UPDRS = Unified Parkinson's Disease Rating Scale.
Data are percentage, mean (SD), or median (interquartile range).

study medication was more common in the naltrexone group (29.2% vs 0%; Fisher exact test, $p = 0.009$). It was reported as mild-moderate intensity in all cases, not associated with vomiting, and did not lead to study discontinuation in any participants. Five participants discontinued study participation before the final study visit (naltrexone = 4, placebo = 1). None of these participants reported new-onset nausea as an adverse event or experienced another adverse event rated likely due to study treatment.

Other adverse events that occurred in >5% of patients and that were more common in the naltrexone group were dizziness (16.7% vs 4.2%) and headaches (20.8% vs 16.7%). An increase or decrease in blood pressure was more common in the placebo group (41.7% vs 25%).

DISCUSSION The results of this study were negative for the efficacy of naltrexone for the treatment of ICDs in PD using a clinician-based rating of global improvement. However, the study lacked the statistical precision to exclude an important difference in response rates between naltrexone and placebo. Using a patient-completed, PD-specific assessment of ICD rating scale, naltrexone treatment was associated with a decrease in ICD symptoms compared with placebo.

One possible explanation for the discrepancy in the findings on the 2 outcome measures is that it is easier to detect a significant difference on a rating scale (continuous measure) compared with a global rating (dichotomous outcome) because the continuous measure contains more information and provides better power.

The completers analyses were consistent with the intent-to-treat analyses. Although not significant, the response rates in the completers and intent-to-treat analyses were numerically higher by 20% in naltrexone-treated patients, and the placebo response rate and the between-group differences were similar

Table 2 Mixed-effects model for response based on QUIP-RS ICD score

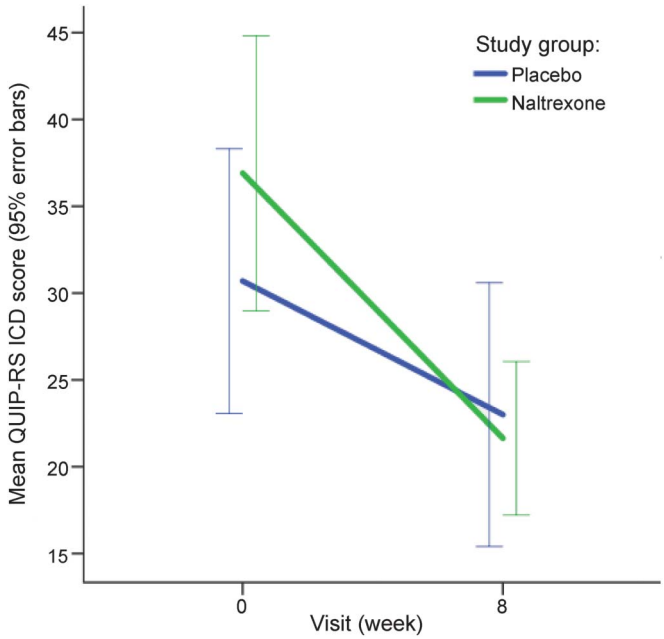
Model[a]	Regression coefficient	*df*	*F*	*p* Value
Intercept	8.44	1, 45	1.36	0.25
Comorbid ICDs	1.63	1, 46	0.87	0.36
History of DBS	−4.65	1, 43	2.76	0.10
Baseline QUIP-RS ICD score	0.81	1, 46	317.46	<0.001
Week 8[b]	−7.55	1, 49	39.64	<0.001
Treatment group[c]	2.31	1, 45	0.71	0.40
Week 8 × treatment group[d]	−7.37	1, 49	4.26	0.04

Abbreviations: DBS = deep brain stimulation; *df* = degrees of freedom; ICD = impulse control disorder; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale.
[a] Type III tests in the mixed-effects model with repeated measures of QUIP-RS ICD score as dependent variable, and diagnosis of comorbid ICDs at baseline, history of deep brain stimulation, baseline QUIP-RS ICD score, week 8, treatment group, and week 8 × treatment group entered as independent variables.
[b] Regression coefficient for week 8 is the estimated decrease of QUIP-RS score at end of study (week 8) for the placebo group (reference group).
[c] Regression coefficient for treatment group is the estimated difference of baseline (week 0) QUIP-RS scores between treatment and placebo groups.
[d] Regression coefficient for week 8 × treatment group is the estimated difference of decrease of the QUIP-RS score at week 8 between treatment and placebo groups. Thus, the estimated decrease of the QUIP-RS score for the treatment group at week 8 is −14.92 (−7.55 minus 7.37).

to those reported in antidepressant clinical trials.[35] In addition, in both completers and intent-to-treat analyses, the decrease in QUIP-RS ICD score over time was approximately twice as great in the naltrexone group.

Regarding exploratory analyses, naltrexone treatment was associated with a greater decrease in novelty-seeking personality traits, although it must be noted that the instruments used were designed to measure stable personality traits, not to detect changes over time. Previous research has demonstrated that patients with PD and ICDs have elevated novelty-seeking traits compared to patients with PD who do not have ICDs,[3,36] and the preliminary results from this study suggest that these traits represent state symptoms that are modifiable.

Figure 2 Change in QUIP-RS ICD score by treatment assignment



ICD = impulse control disorder; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale.

The nonstatistically significant difference in UPDRS scores between the placebo and naltrexone groups is consistent with previous findings of good motor tolerability for naltrexone in patients with PD.[17] In addition, the adverse events that occurred in this study were consistent with the results from a large open-label safety profile study of naltrexone in patients with alcoholism, in which the 2 most common side effects were nausea (9.8%) and headache (6.6%).[37]

There have now been 3 controlled studies for the treatment of ICDs in PD. The first was a placebo-controlled, crossover study of amantadine,[9] and the second was a study of cognitive-behavioral therapy,[38] both yielding positive findings. However, amantadine has also been associated with presence of ICDs in PD,[10] and its role in the treatment of ICDs in this population remains controversial. Cognitive-behavioral therapy can be combined with pharmacologic treatments.

Study limitations include (1) use of a single site; (2) a predominance of patients with compulsive eating compared with other ICDs, which limits generalizability; (3) statistical (DBS and comorbid ICDs) or numerical (baseline QUIP-RS ICD score) between-group differences in baseline values in variables that necessitated adding covariates to the statistical models

but still may have helped account for changes in QUIP-RS scores over time; and (4) only having 2 time points (baseline and end of study) for the QUIP-RS, which prevented examining the course of change over the study period.

The results of this preliminary study support further research with naltrexone (including at higher doses) or other opioid antagonists (e.g., nalmefene) for the treatment of ICDs in PD. In addition, other novel treatments to be considered for this condition include medications targeting the glutamate system (e.g., *N*-acetylcysteine[39]) and the possibility of DBS of the nucleus accumbens. An important consideration for future studies in this area includes having an appropriate primary outcome measure that will be sensitive to changes in symptoms.

AUTHOR CONTRIBUTIONS

K.P., S.X.X., and D.W. designed the study. K.P., J.M., and D.W. performed study assessments. K.P., S.X.X., and D.W. analyzed the data. M.S., H.H., A.S., J.E.D., and J.M. recruited patients, verified a PD diagnosis, and recorded clinical data. K.P. and D.W. drafted the manuscript. All authors edited the manuscript for accuracy and content.

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DISCLOSURE

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