Randomized, proof-of-concept trial of low dose naltrexone for patients with breakthrough symptoms of major depressive disorder on antidepressants∗

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ABSTRACT

Background: Given the proposed dopaminergic mechanism of low-dose naltrexone (LDN), we examined its efficacy as augmentation for depressive breakthrough on pro-dopaminergic antidepressant regimens.

Methods: 12 adults (67% female, mean age = 46 ± 12) with recurrent DSM-IV major depressive disorder (MDD) on dopaminergic antidepressant regimens (stimulants, dopamine agonists, bupropion [≥300 mg/day], aripiprazole [≥2.5 mg/day], or sertraline [≥150 mg/day]) were randomized to naltrexone 1 mg b.i.d. (n=6) or placebo (n=6) augmentation for 3 weeks.

Results: All subjects completed the trial. Hamilton Depression Rating Scale (HAM-D-17) scores (primary outcome measure) decreased from 21.2 ± 2.0 to 11.7 ± 7.7 for LDN, from 23.7 ± 2.3 to 17.8 ± 5.9 for placebo (Cohen’s d=0.62; p=0.03 between treatment groups). HAM-D-28 scores decreased from 26.2 ± 4.0 to 12.0 ± 9.8 for LDN, from 26.3 ± 2.6 to 19.8 ± 6.6 for placebo (d=1.15; p=0.097). Montgomery-Asberg Depression Rating Scale (MADRS-15 item) scores decreased from 30.4 ± 4.9 to 12.2 ± 8.4 for LDN, from 30.7 ± 4.3 to 22.8 ± 8.5 for placebo (d=1.45; p=0.035). MADRS-15 item scores decreased from 36.6 ± 6.2 to 13.2 ± 8.8 for LDN, from 36.7 ± 4.2 to 26.0 ± 10.0 for placebo (d=1.49; p=0.035). Clinical Global Improvement Scale-Severity (CGI-S) scores decreased from 4.3 ± 0.5 to 3.0 ± 1.1 for LDN, from 4.3 ± 0.5 to 4.0 ± 0.6 for placebo (d=1.22; p=0.064).

Limitations: Small study; restrictions on allowed antidepressants.

Conclusion: LDN augmentation showed some benefit for MDD relapse on dopaminergic agents. Confirmation in larger studies is needed.

1. Introduction

Managing depressive breakthrough during treatment of major depressive disorder (MDD) is a challenging and understudied area. Between 40–60% of antidepressant responders will relapse within one year (Ramana et al., 1995; Rush et al., 2006a, 2006b). Continued antidepressant therapy lowers the risk of MDD relapse and recurrence compared to placebo substitution (Geddes et al., 2003), but 20–80% of antidepressant responders receiving maintenance therapy will have recurrence within 1–5 years (Ramana et al., 1995; Montgomery et al., 1988; Peselow et al., 1991). By 15 years, cumulative recurrence rates may reach 85% (Mueller et al., 1999). The literature on depressive breakthrough management consists predominantly of non-rigorous case series, surveys and open trials with heterogeneous study samples (Alpert and Fava, 2004). Randomized controlled efficacy trials of medication augmentation for depressive breakthrough are lacking. Given the limited efficacy of available treatments, high relapse rates, and decline in antidepressant development (Shorter and Tyrer, 2003), novel approaches to managing depressive breakthrough are needed.

Naltrexone hydrochloride is a competitive antagonist (possibly exerting inverse agonistic effects) at mu and delta opioid receptors. At oral doses of 50–100 mg, it can reverse opioid overdoses and treat alcohol addiction. Paradoxically, ultra-low dose naltrexone (< 1 μg) enhances the effects of opioid agonists. Naltrexone binds to the C-terminal pentapeptide of the scaffolding protein filament A with strong avidity (Kd < 5 pm), which may prevent or reverse a change in G-protein signaling in G-coupled receptor systems, such as the mu opioid receptor, after prolonged stimulation by agonists (Wang et al., 2008).


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© Drs Soskin and Fava contributed equally to the inception, hypotheses, and design that formed the basis of the study and are considered as co-senior authors.

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Filamin A is also found in dopaminergic D2 and D3 receptors, which led Bear and Kessler to propose that low (LDN) or ultra-low (ULDN) doses of naltrexone might reverse or prevent desensitization to D2/3 agonists (Bear and Kessler, 2014a, 2014b). This was tested in Restless Leg Syndrome (RLS), thought to result from a deficiency of D2/3 compared to D1 agonism, and typically treated with D2/3 agonists pramipexole or ropinirole. Periodic Limb Movements of Sleep measurements confirmed that ULDN allowed equivalent control of limb movements at half the prior dose of D2/3 agonists. Although the naltrexone dose was 0.15 μg, the effect was retained at 100 μg and 1 mg (Bear and Kessler, 2014a, 2014b). Thus, naltrexone proved effective for RLS, putatively by facilitating sensitization of D2/3 agonists.

The pathophysiology of depression is thought to involve abnormal dopaminergic D2 receptor function, as well as abnormalities in cortico-basal ganglia reward systems (Dunlop and Nemeroff, 2007). A review by Soskin et al. (2013) notes that individuals with MDD may show reduced concentrations of homovanillic acid (HVA), a dopamine metabolite, in cerebrospinal fluid (Roy et al., 1986; Lambert et al., 2000); reduced striatal dopamine transporter density (Klimek et al., 2002); and increased D2/D3 receptor striatal binding (Di Mascio et al., 1998; Meyer et al., 2006), though not all data support these mechanisms (Parsey et al., 2001; Hirvonen et al., 2008). An additional link to depression is the observation that following successful treatment of depression with SSRIs, a D2 antagonist (sulpiride 200 mg) produced a return of depressive symptoms (Willner et al., 2005); analogous observations in an animal model of depression, reversed by trycyclic antidepressants, suggested that preventing D2 receptor desensitization was essential to effective treatment with SSRIs or SNRIs (Willner, 2002). Thus antidepressants may foster the sensitization of D2 receptors, and ULDN or LDN may exert antidepressant effects by enhancing dopaminergic signaling.

Currently, data on ULDN or LDN as a treatment approach to mood disorders are scarce, but anecdotal evidence and multiple clinical trials of LDN in different conditions have suggested beneficial mood effects (Bear and Kessler, 2014a, 2014b). For instance, LDN reduces symptoms of fibromyalgia, many of which overlap with core symptoms of major depressive disorder (MDD) (Younger and Mackey, 2009). Similarly, in cancer patients naltrexone reduced depression-like side effects of treatment with interferon-α (Valentine et al., 1995). More recently, Almatroudi et al. (2015) observed that combined administration of buprenorphine (1 mg/kg) with naltrexone (1 mg/kg) produced antidepressant-like responses in mice in the forced swim test and novelty induced hypophagia task.

While the pathophysiology of antidepressant tachyphylaxis (“poop-out”) is not yet fully understood, serotonergic antidepressant “apathy syndrome” has been hypothesized to arise from inhibitory effects of serotonin upregulation on dopamine transmission in the prefrontal cortex (Dunlop and Nemeroff, 2007). Therefore, tachyphylaxis might be reversed by LDN via dopaminergic enhancement or activation of “hedonic hotspots” in the mesolimbic reward circuitry involving G-coupled excitatory opioid receptors (Roshanpour et al., 2009). Naltrexone’s low cost (< $40/month), safety, and mild side effect profile also support a proof-of-concept study (Younger and Mackey, 2009).

We carried out a pilot double-blind, randomized, controlled study of LDN 1 mg b.i.d. versus placebo augmentation in MDD patients who relapsed on dopaminergic agents. The primary aim was to test the hypothesis that patients experiencing depressive breakthrough would demonstrate greater improvement in their depression when supplementing their current antidepressant regimen with LDN versus placebo, with no significant difference in side effects.

2. Methods

The study was approved by our Institutional Review Board (IRB), written informed consent was obtained, and the study was registered at ClinicalTrials.gov (identifier: NCT01874951). Boston area men and women with MDD were recruited from 01/13/2014-11/11/2014 via IRB-approved newspaper, television, internet, and radio ads initiated by MGH and Boston Clinical Trials (BCT).

Inclusion Criteria included: age 18–65; written informed consent; meeting Structured Clinical Interview for DSM-IV (SCID-I/P) (First et al., 1995) criteria for current MDD; 17-item Hamilton Depression Rating scale (HAM-D-17) (Hamilton, 1960) score ≥18 at the screening visit; Quick Inventory of Depressive Symptomatology – Self-Rated (QIDS-SR) (Trivedi et al., 2004) score ≥12 at screen and baseline visits; having received treatment with either an SSRI plus a dopaminergic agent, or with a dopaminergic antidepressant in adequate doses per MGH Antidepressant Treatment Response Questionnaire (ATRQ) (Chandler et al., 2010), achieved remission per American College of Neuropsychopharmacology (ACNP) Task Force guidelines (Rush et al., 2006a, 2006b) for ≥3 months at any time on the current antidepressant regimen, and then having a recurrence, without dose change for at least the past 4 weeks. We did not systematically assess the total number of historical relapses. A minimum of one documentable relapse was required. Details of past antidepressant therapies administered prior to the patients’ current regimen were inquired about, but were not a factor in the inclusion or exclusion criteria.

Acceptable dopaminergic agents included: stimulants from the amphetamine or methylphenidate families; dopamine agonists (e.g. pramipexole); bupropion at ≥300 mg/day to ensure significant dopamine reuptake inhibition; low-dose aripiprazole (≥2.5 mg/day), and sertraline (an SSRI with relevant dopamine reuptake inhibiting properties at doses ≥150 mg/day) (Stahl, 2011). Although duloxetine possesses norepinephrine reuptake inhibition (NRI) relevant to prefrontal uptake of dopamine (DA) (Stahl, 2011), the latter mechanism is not thought to contribute significantly to duloxetine’s antidepressant effect; therefore duloxetine was allowed only in combination with a dopaminergic agent.

Exclusion Criteria included: no longer meeting DSM-IV criteria for MDD during the baseline visit; substance use disorders active within the last six months; any current or past bipolar or psychotic disorder or psychotic features (other psychiatric conditions such as anxiety disorders were allowed, provided that they did not constitute the primary source of the patient’s depressive symptomatology and general pathology); history of antidepressant-induced hypomania; demonstrating a > 25% decrease in depressive symptoms per the QIDS-SR score between screen and baseline; inadequate exposure time or dose of current antidepressant regimen; compliance rate < 80% of doses; requiring excluded medications; history of naltrexone intolerance; serious suicide or homicide risk, per evaluating clinician; pregnancy or women of child bearing potential who are not using a medically accepted means of contraception; unstable medical illness; multiple sclerosis (MS); insulin-dependent diabetes mellitus; seizure disorder; untreated hypothyroidism; cerebrovascular accident (CVA) or any structural brain lesion; cancer within the past 5 years (except for non-melanoma skin cancers); evidence of Post-Chemotherapy Cognitive Impairment (PCCI).

Concomitant benzodiazepine and non-benzodiazepine sedative-hypnotics were allowed if subjects were on a stable regimen for at least 2 weeks prior to baseline at doses no greater than the following or their equivalent: clonazepam 3.0 mg qd and zolpidem 10 mg qhs; adequate thyroid replacement stable for ≥6 months was acceptable, as was estrogen replacement or oral contraceptives. Because antipsychotic agents may interfere with the pro-dopaminergic effect of naltrexone via dopamine receptors (primarily D1 and D2 receptors), typical and atypical antipsychotic drug were exclusionary, except low-dose (≤2.5 mg/day) aripiprazole which is a D2 receptor partial (and selective) agonist rather than a D2 blocker; quetiapine ≤50 mg/day and trazadone ≤300 mg/day were allowed for insomnia.

Exclusionary agents included all typical antipsychotics except as
noted above; ziprasidone, risperidone, aripiprazole, and lurasidone; gabapentin, because of potential effects on dopamine release; alpha-2 antagonists (e.g., tizanidine), which can produce depression; dietary supplements with putative central nervous system activity, including SAMe, St. John’s Wort, dehydroepiandrosterone (DHEA), inositol, Ginko biloba and omega-3-fatty acids.

A full medical and psychiatric history was obtained, and a physical examination was performed at screen by a study physician. Vital signs (weight, and standing and supine pulse and blood pressure) were recorded at each visit. A urine pregnancy test (for women of child-bearing potential) and urine drug test for prohibited agents, were conducted at screening. Because changes in liver enzymes have not been found with LDN, liver function tests (LFTs) were assessed only at screening and at the conclusion of the follow up period (6 weeks) (Younger and Mackey, 2009).

The primary efficacy measure was the change in HAM-D-17 score. The 28-item Hamilton Depression Scale (HAMD-28) was also used, to allow assessment of impact of LDN on various additional depressive symptoms. Response was defined as a 50% or greater reduction in HAM-D-17 score from baseline. Remission was defined as a HAM-D-17 score < 8 at endpoint. The Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), 10- and 15-item versions were used as secondary outcome measures, given that they cover certain dimensions of MDD that are not covered by the HAM-D-17, e.g. concentration. This gave a more thorough characterization of the full effects of the LDN therapy. The Clinical Global Impressions-Severity and Improvement (CGI-S, CGI-I) (Guy, 1976) were also used to determine overall improvement, with “clinical response” defined as CGI-I of 1 or 2 (“much” or “very much” improved) at endpoint.

Other scales that were administered but not reported here include the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (Fava et al., 2009); the Massachusetts General Hospital Sexual Functioning Questionnaire (Fava et al., 1998); the Quality of Life Satisfaction Questionnaire-short form (Q-LES-Q) (Endicott et al., 1993); and the Sheehan Disability Scale (Leon et al., 1992).

Screened and eligible patients returned one week later for a baseline visit and were randomized consecutively to double-blind treatment with placebo or LDN 1 mg b.i.d. (provided by PharmoRx). The randomization list was generated by an online randomization program and maintained by the research pharmacist. Subjects were treated for 3 weeks, with weekly assessments. Three weeks was selected as the treatment period because preliminary evidence (Bear and Kessler, 2014a, 2014b) suggested that this was an adequate period to assess efficacy. All subjects were required to continue on their baseline antidepressant regimen without changes for the duration of the study; they were likewise asked not to modify any other allowed baseline medications that they had been taking prior to entering the study. Adherence was determined by weekly pill counts; protocol violation was defined as less than 80% adherence.

Side effects were assessed at every visit using the Systematic Assessment for Treatment Emergent Effects-Specific Inquiry (SAFTEE-SI) scale (Levine and Schooler, 1992) and categorized by severity as: 0-none, 1-mild, 2-moderate, 3-severe. Because some SAFTEE items could be present at baseline, particularly in a sample of subjects taking antidepressants that could themselves produce side effects, we defined as treatment-emergent any SAFTEE side effect for which severity increased by two or more levels (e.g. from none to moderate or from mild to severe) from baseline (Mischoulon et al., 2014). Frequency of side effect was based on the number of patients reporting the side effect at any time during the study.

Suicidal ideation was assessed at each visit using the HAM-D. Subjects considered to be at high risk for suicide were discontinued and referred for further evaluation and hospitalization if clinically indicated. Subjects were also discontinued for any emergence of hypomania, mania, or psychosis; a CGI-I score greater than 5 (e.g., score of 6 or 7); evidence of illicit drug use or problematic alcohol use.

At the end of the double-blind study, both responders and non-responders who completed the double-blind phase had the option of receiving open-label adjunctive treatment with LDN for 3 more weeks.

2.1. Statistical methods

Paired and independent samples t-tests and their nonparametric counterparts (Wilcoxon’s signed ranks and Mann-Whitney U tests) were used to examine and compare outcomes for each treatment arm. All analyses were two-tailed. Response and remission rates, and emergence of side effects were compared by Fisher’s exact test. Effect sizes (ES) were calculated by Cohen’s d (Cohen, 1988), for between-subjects comparisons (changes in depression scales from baseline to end for LDN vs. placebo) and for within-subjects comparisons (changes in depression scales from baseline to end for each separate treatment group). Correlation coefficients were calculated for use in within-subjects comparisons. Statistical analyses were carried out using SPSS version 17.0 (SPSS Inc, Chicago, Illinois).

3. Results

A total of 21 prospective subjects were screened. Nine were excluded for the following reasons: sub-threshold HAM-D scores (n=3); too recent changes in medication regimen (n=2); cerebrovascular accident in past 5 years (n=1); no history of past treatment response (n=1); inappropriate antidepressant (n=1); antidepressant treatment dose too low and duration too short (n=1). Twelve patients (67% female, mean age =45 ± 12) were randomized to LDN (n=6) or placebo (n=6) augmentation for 3 weeks. Ten of the 12 subjects took bupropion as the primary antidepressant (9 at doses ≥300 mg); five of these subjects used bupropion SR (at 200 mg, 300 mg, 300 mg, 400 mg, 450 mg), and 5 used bupropion XL (300 mg, 300 mg, 300 mg, 375 mg, 450 mg). Four subjects taking bupropion took it as monotherapy; 1 also took sertraline, mirtazapine, methylphenidate, and amantadine; other secondary antidepressants included duloxetine (n=1), venlafaxine (n=1), escitalopram (n=1), levotyphroxine (n=1), sertraline (n=1) and mirtazapine (n=1). One subject took sertraline (150 mg) monotherapy, and 1 took fluoxetine in combination with aripiprazole. See Table 1 for regimen comparisons between treatment groups.

All subjects completed the study. Non-parametric test results (Wilcoxon signed ranks and Mann-Whitney U [MWU]) were summarized here, and both parametric and non-parametric test results are detailed in Table 2. Decrease in HAM-D-17 scores for LDN (Wilcoxon z=−2.21, p=0.027) and placebo (Wilcoxon z=−1.99, p=0.046), did not differ significantly from each other by Mann-Whitney U (MWU) test (MWU z=−1.04, p=0.30, Cohen’s d=0.62; Fig. 1). The difference in decrease in HAM-D-28 scores for LDN (Wilcoxon z=−2.02, p=0.043) and placebo (z=-1.58, p=0.11) did not reach significance (MWU z=−1.66, p=0.097, d=1.15; Fig. 1). Decrease in MADRS-10 scores for LDN (Wilcoxon z=−2.02, p=0.043) and placebo (z=−1.78, p=0.075) differed significantly (MWU z=−2.10, p=0.035, d=1.45; Fig. 2). Decrease in MADRS-15 scores for LDN (Wilcoxon z=−2.03, p=0.042) and placebo (Wilcoxon z=−1.99, p=0.046), differed significantly (MWU z=−2.11, p=0.035, d=1.49; Fig. 2). Difference in decrease in CGI-I scores for LDN (Wilcoxon z=−2.07, p=0.038) and placebo (z=−1.00, p=0.32) did not reach significance (MWU z=−1.86, p=0.064, d=1.22; Fig. 3). CGI-I scores at 3 weeks for LDN (2.2 ± 1.2) and placebo (3.5 ± 0.8) did not differ significantly (MWU z=−1.93, p=0.053, d=1.0; Fig. 3). Within-subjects comparisons for change in the outcome measures in each separate treatment group yielded more robust effect sizes for the LDN group (Cohen’s d ranged from about 1.9−4.0) than for the placebo group (Cohen’s d ranged from about 0.3−1.4), as detailed in Table 2.

Response rates based on HAM-D-17 score improvement were 50%
Abbreviations: LDN: Low-dose naltrexone; PBO: Placebo

Demographics and Baseline Antidepressant Regimens of Study Sample.

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Abbreviations: LDN: Low-dose naltrexone; PBO: Placebo

<sup>a</sup> Also taking levothyrinone.

<sup>b</sup> Also taking methylphenidate and amantadine.

for LDN and 17% for placebo (χ²=1.5, Fisher’s p=0.55), with an odds ratio (OR) of response of 5.0 in favor of LDN. Remission rates were 50% for LDN and 0% for placebo (χ²=4.0, Fisher’s p=0.18) (Table 2). The open label follow up of the patients assigned to LDN showed continued improvement over the additional 3 weeks (data not shown).

Post hoc analyses of each individual HAM-D and MADRS item were carried out to compare changes and potentially explain the differences in outcomes of HAM-D and MADRS. Changes in HAM-D items 6 (late insomnia; MWU z=−2.02, p=0.043), 7 (interest; MWU z=−2.67, p=0.008), and 13 (energy; MWU z=−2.02, p=0.043) differed significantly between LDN and placebo. Changes in MADRS items 1 (reported sadness; MWU z=−2.21, p=0.027), 2 (apparent sadness; MWU z=−2.60, p=0.009), and 6 (concentration; MWU z=−1.99, p=0.047), differed significantly between LDN and placebo, with item 8 (interest; MWU z=−1.88, p=0.06) trending to significance. Bonferroni correction would result in a required p <0.003 for the HAM-D-17, and a p < 0.005 for the MADRS-10, which would render all comparisons nonsignificant.

Only 8 side effects were reported with LDN compared to 12 with placebo. No side effect attained a frequency >33% (Table 3). Emergence of any side effects did not differ significantly between treatment arms, thus no correction for multiple comparisons was needed. No subject discontinued because of side effects.

4. Discussion

Neither the main outcome measure (HAM-D) or global outcome measure (CGI) presented a significant improvement for the LDN group over placebo, with only the MADRS attaining a significant separation between LDN and placebo. Nonetheless, effect sizes were consistently strong in all outcome measures, in favor of LDN. Furthermore, within-subjects effect sizes based on pre- and post-treatment measurements were consistently stronger for LDN than for placebo in all outcome measures, with the narrowest differential for the HAM-D (Table 2).

The findings reported were originally intended to serve as an interim analysis on the first 12 patients recruited in a study that originally planned to recruit up to 36 subjects. An initial power analysis at the time of protocol development suggested that with 6 patients in each treatment group for the interim analysis, we could expect a 79% chance of achieving significance (2-sided p < 0.05) if the true response rate to LDN was 80% and the true placebo response rate was 20%. Depending on how close the interim analysis results came to the model, a decision would be made as to how many more subjects would be needed for the full study. The observed response rate differential was not as robust as predicted in the model (50% for LDN vs. 17% for placebo). However, the effect sizes for LDN versus placebo based on the different outcome measures were all very strong, ranging from d=0.62 to d=1.49, with significant advantages for LDN on the MADRS-10 and MADRS-15 scales, and trends to significance on the HAM-D-28, CGI-S, and CGI-I scales (Table 2). With regard to within-group changes (pre- and post-treatment) in the outcome measures, the effect sizes for LDN ranged from d=1.96 to d=4.04, all reaching statistical significance. For placebo, effect sizes were consistently more modest, from d=0.55 to d=1.45, with only two measures barely reaching significance at p=0.046 (Table 2).

Because recruitment challenges required us to implement more aggressive advertising and collaborate with the independent site Boston Clinical Trials, a greater expenditure of financial resources than originally budgeted for was required. By the time we completed the 12 patients, the original budget was more or less depleted. At that point the sponsor had to decide between raising additional funds to recruit more patients or halting the study to begin seeking funding for a larger confirmatory study.

Based on the observed difference in improvement in the HAM-D-17 scale, which showed the least robust effect between treatment groups, a conservative power analysis was conducted to guide the development of a follow-up study. Assuming a desired significance level of p < 0.05, standard deviation of 6 points, difference in means of 4 points, and a desired power of 0.8, a sample of at least 74 patients would give the desired power of 0.8, a sample of at least 74 patients would give significant separation in all the above outcome measures, assuming the pattern from these 12 patients is retained. This would also be expected to produce significant separation based on response rates (improvement of HAM-D-17≥50%). Given the strong effect sizes, and the consistently significant changes observed for LDN, the sponsors decided it would be more cost-effective to end the pilot study and begin plans for a larger confirmatory trial.

To better understand why the HAM-D scale did not produce such a robust change as the MADRS, we compared changes in individual items. Our analysis suggested that the MADRS was more sensitive to changes in sadness and concentration, the HAM-D was more sensitive to changes in insomnia and energy, and both were sensitive to changes in interest. If the MADRS was a more sensitive instrument for this particular sample, it may be due to LDN having a stronger effect on mood and concentration, which could be attributed to dopaminergic actions.
The Bear and Kessler model (Bear and Kessler, 2014a, 2014b) suggests that dopaminergic signaling is related to hedonic tone. Our findings appear consistent with that model, given the improvement in interest and pleasure found in patients taking LDN. Interestingly, no subjects taking LDN complained of loss of libido, problems with arousal, or anorgasmia. This raises the question of whether naltrexone’s dopaminergic mechanism may have a protective effect against antidepressant-induced sexual dysfunction, and deserves further investigation.

The mean age of our study subjects was 45 ± 12 years of age (range 25–64), reflecting the typical distribution seen in our antidepressant studies. Not much is known regarding how age may affect differential response to antidepressants of varying mechanisms. While our sample is too small to allow for any conclusions regarding age’s impact on treatment response, the good tolerability provided by the low dose of naltrexone augmentation suggests that this approach, if verified in larger studies, could be a good strategy for older patients who are more vulnerable to antidepressant side effects.

We did not correct for multiple comparisons by the different instruments because one of the goals of this pilot study was to use sensitivity in assessing clinical outcomes in a larger, more rigorous trial. Regarding the individual item comparisons from the HAM-D and MADRS, we did not correct for multiple comparisons by the different failure to reach statistical significance. It is unfortunate that we were not able to recruit the full projected complement of study subjects, which would have strengthened the investigation.

The sample size was very small, and this may have accounted for most findings failing to reach statistical significance. It is unfortunate that we were not able to recruit the full projected complement of study subjects, which would have strengthened the investigation.
We did not obtain detailed data about the total number of relapses or recurrences experienced by the subjects. Likewise, treatments administered prior to the patients’ current regimen were not a factor in the inclusion or exclusion criteria. It is possible that individuals with greater treatment resistance, such as having more failed trials and/or more recurrences, may be less likely to respond to this approach, and future studies should document these factors systematically so as to characterize the population most likely to respond to this intervention.

The short treatment period of 3 weeks was selected in part because preliminary anecdotal evidence suggested a relatively rapid effect of LDN (Bear and Kessler, 2014a, 2014b). Ideally, a longer double-blind treatment period might have been more desirable, so as to observe whether the initial effect was sustained, increased, or lost. The follow-up period of 3 weeks, while less rigorous, suggested that improvement was maintained (data not shown). Budgetary considerations also made a longer double-blind treatment period less feasible.

Another important limitation is the restrictions on the allowed antidepressants. Because we focused on antidepressants with dopaminergic activity, we do not know whether this strategy may work with antidepressants that lack a significant dopaminergic effect. The dopaminergic mechanism proposed for LDN appears consistent with our findings. However, naltrexone as a non-selective-opioid antagonist has several diverse effects on monoaminergic systems, and several studies have shown that opioid receptor antagonists affect glutamatergic, nitrergic, and inflammatory pathways among others (Lutz et al., 2013). Naltrexone has also been shown to inhibit tumor necrosis factor alpha (TNF-α) production (Greenelch et al., 2004), and exert apparent anti-inflammatory benefits in Crohn’s disease (Smith et al., 2007); these potential anti-inflammatory effects could also contribute to antidepressant effects. Likewise, primate studies have shown that monkeys with induced serum sickness and concurrent elevated inflammatory status appear depressed (Felger et al., 2015), and in human studies the inflammatory cytokine interferon-α produces depressive behavior along with changes in presynaptic striatal dopamine function, suggesting decreased dopamine synthesis or release (Capuron et al., 2012). These findings suggest a link between inflammation, dopamine signaling and depression, and encourage further investigation in this regard.

Other proposed mechanisms that could be relevant to depression include effects on toll-like receptor 4 (TLR4) that may impact on neuropathic pain (Hutchinson et al., 2008). We must also acknowledge the question of whether a non-DA related opiate-mediated effect is...
Given the diverse range of documented effects of naltrexone, many possible interactions with antidepressant regimens could be postulated. Future studies should include at least one other group receiving non-dopaminergic regimes. By comparing larger groups of LDN + dopaminergic antidepressants against LDN + non-dopaminergic antidepressants, it would make it easier to address whether naltrexone reverses dopaminergic desensitization. Nonetheless, by focusing initially on the putative pro-dopaminergic effect of LDN, we hoped to pave the way for more mechanistically oriented investigations that would both confirm clinical efficacy as well as allow for measurement of biological markers of effect.

In summary, our findings suggest that LDN may have beneficial effects and good tolerability as an augmentation agent for individuals with MDD who relapse on a regimen including dopamine enhancing agents. Confirmation studies are currently in development.

Contributors

Dr. Mischoulon conducted the study, wrote the first draft of the manuscript, and participated in the statistical analysis. Ms Hylek, and Drs. Yeung, Cusin, Ionescu, and Alpert assisted with the writing of the manuscript. Ms. Clain and Dr. Baer directed the statistical analysis. Drs. Soksin and Fava contributed to the inception, hypotheses, and design that formed the basis of the study, and assisted with the writing of the manuscript; they are considered as co-senior authors. Dr. Fava supervised the entire project.

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The study was sponsored by PharmoRx Therapeutics, who provided funding, drug, and placebo. Only the authors were responsible for the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript for submission. The sponsors played no role in any of the above.

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References


