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## Combining a dopamine agonist and selective serotonin reuptake inhibitor for the treatment of depression: A double-blind, randomized pilot study

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### Abstract

**Background**—Antidepressants that act on two or more amine neurotransmitters may confer higher remission rates when first-line agents affecting a single neurotransmitter have failed. Pramipexole, a dopamine agonist, has antidepressant effects in patients with major depressive disorder (MDD). This pilot study examined the efficacy and safety of combination therapy with pramipexole and the selective serotonin reuptake inhibitor (SSRI) escitalopram in MDD.

**Methods**—In this double-blind, controlled, pilot study, 39 patients with DSM-IV MDD who had failed to respond to a standard antidepressant treatment trial were randomized to receive pramipexole ( $n=13$ ), escitalopram ( $n=13$ ), or their combination ( $n=13$ ) for six weeks. Pramipexole was started at 0.375 mg/day and titrated weekly up to 2.25 mg/day; escitalopram dosage remained at 10 mg/day. The primary outcome measure was the Montgomery–Asberg Depression Rating Scale (MADRS).

**Results**—Subjects receiving pramipexole monotherapy had significantly lower MADRS scores than the combination group ( $p=0.01$ ); no other primary drug comparisons were significant. The combination group had a substantially higher dropout rate than the escitalopram and pramipexole groups (69%, 15%, 15%, respectively). Only 15% of patients in the combination group tolerated regularly scheduled increases of pramipexole throughout the study, compared with 46% of patients in the pramipexole group.

**Limitations**—Group size was small and the treatment phase lasted for only six weeks.

**Conclusions**—The combination of an SSRI and a dopamine agonist was not more effective than either agent alone, nor did it produce a more rapid onset of antidepressant action. Combination therapy with escitalopram and pramipexole may not be well-tolerated.

### Keywords

Depression; Escitalopram; Pramipexole; Combination treatment; Augmentation strategies

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### Conflict of interest

All other authors report no conflict of interest, financial or otherwise.

## 1. Introduction

While several treatments are available for major depressive disorder (MDD), the rate of remission associated with first-line antidepressants is as low as 30–40% (Nemeroff et al., 2008; Trivedi et al., 2006). Both newer and older antidepressants typically exert their primary biochemical effects by increasing intrasynaptic levels of monoamines, most often serotonin and/or norepinephrine (Berton and Nestler, 2006; Insel and Charney, 2003). Newer agents often have fewer side effects, but have not demonstrated improved efficacy over older, traditional antidepressants (e.g., tricyclic antidepressants) (Gartlehner et al., 2008, 2011). Some evidence suggests that newer antidepressants acting on two or more amine neurotransmitters may produce higher rates of remission when first-line agents that affect a single neurotransmitter have failed, but the remission rate remains below 40% (Baldomero et al., 2005; Lenox-Smith and Jiang, 2008; Papakostas et al., 2007; Poirier and Boyer, 1999; Rush et al., 2006).

Given the limited success associated with currently available antidepressants, it would be reasonable to investigate other classes of psychotropic drugs that affect processes outside the serotonin-norepinephrine dyad. A common strategy used to improve treatment response is the combination of a first-line treatment with one or more additional pharmacologic agents (American Psychiatric Association, 2010). Combining medications with dissimilar mechanisms of action may have a synergistic or additive effect that would be superior to that of an antidepressant that targets a single mechanism of action.

Escitalopram is an established selective serotonin reuptake inhibitor (SSRI) approved by the Food and Drug Administration (FDA) for the treatment of MDD in adults and adolescents, as well as Generalized anxiety disorder (Forest Laboratories, 2011). Studies have shown that it is highly selective for the serotonin transporter (Owens et al., 2001), and has been reported – though not established – to be one of the fastest acting SSRIs (Gorman et al., 2002; Montgomery et al., 2004). It also has a favorable side effect profile (Baldwin et al., 2006; Montgomery et al., 2004; Murdoch and Keam, 2005; Nierenberg et al., 2007).

Pramipexole, a dopamine agonist, has preference for the D<sub>3</sub> receptor and less affinity for the D<sub>1</sub>, D<sub>2</sub>, and D<sub>4</sub> receptors (Gerlach et al., 2003). The D<sub>3</sub> receptor is densely distributed in the mesolimbic system and has been implicated in the motor and anhedonic symptoms of depression (Zarate et al., 2004). It is also known to have antioxidant activity, inhibits mitochondrial permeability transition, and up-regulates the expression of the neuroprotective factor B-cell lymphoma-2 (Bcl-2) (Cassarino et al., 1998, 2000; Le and Jankovic, 2001; Takata et al., 2000). Pramipexole is FDA-approved for the treatment of Parkinson's disease and Restless Leg Syndrome (Antonini et al., 2010; Aurora et al., 2012); it has also shown antidepressant effects in patients with MDD, in patients with bipolar depression, and in Parkinson's patients comorbid for MDD (Barone et al., 2006; Cassano et al., 2004; Corrigan et al., 2000; Goldberg et al., 2004; Inoue et al., 2010; Lattanzi et al., 2002; Moller et al., 2005; Perugi et al., 2001; Rektorova et al., 2003; Sporn et al., 2000; Zarate et al., 2004).

Randomized placebo-controlled trials demonstrated the efficacy of pramipexole in treating mood disorders. In an eight-week, double-blind, placebo-controlled study of 174 subjects with MDD without psychotic features, Corrigan et al. (2000) found that 1.0 mg/day of pramipexole was as effective as 20 mg/day of fluoxetine and superior to placebo. Another trial investigated treatment-resistant subjects with bipolar II depression (Zarate et al., 2004). After an initial six-week phase of treatment with either divalproex sodium or lithium, those who did not respond to the mood stabilizer were randomly assigned to receive augmentation with either pramipexole or placebo. The antidepressant effects of pramipexole began to differentiate from placebo at three weeks; significant symptom reduction was observed at

week six. Mean Montgomery–Asberg Depression Rating Scale (MADRS) scores at the end of six weeks for pramipexole vs. placebo respectively were  $17.2 \pm 8.4$  vs.  $27.6 \pm 7.7$  ( $p=0.01$ ), and mean 17-item Hamilton Depression Rating Scale (HDRS-17) scores at the end of six weeks for pramipexole vs. placebo were  $14.1 \pm 7.1$  vs.  $22.6 \pm 8.6$ , respectively ( $p=0.02$ ). Finally, Goldberg et al. (2004) compared flexible dosing of pramipexole to placebo as an augmentation strategy for patients with bipolar depression who were receiving mood stabilizers but who had not responded to at least two previous antidepressant trials. Eight (67%) of 12 patients taking pramipexole and two (20%) of 10 taking placebo had an improvement of at least 50% on the HDRS. The mean percentage of improvement from baseline HDRS was greater for patients taking pramipexole (48%) than for those taking placebo (21%,  $p=0.04$ ).

The current pilot study examined the value of combined treatment with escitalopram and pramipexole under controlled, double-blind conditions. We hypothesized that combining an SSRI and a dopamine agonist would: (1) be more effective than treatment with either agent alone; and (2) lead to a more rapid onset of antidepressant effects in patients suffering from MDD. We selected the combination of escitalopram and pramipexole because escitalopram is an effective and well-tolerated SSRI, and because pramipexole is a dopamine agonist with antidepressant properties.

## 2. Methods

### 2.1. Subjects

This was a single-center, random assignment, double-blind, preliminary study conducted to assess the efficacy and safety of escitalopram, pramipexole, and the combination of escitalopram plus pramipexole in the treatment of MDD. Subjects with MDD without psychotic features currently experiencing a major depressive episode lasting at least four weeks were evaluated at baseline and weekly for six weeks of acute treatment. Diagnoses were established by clinical evaluation and by the Structured Clinical Interview for DSM-IV (SCID) (First et al., 2001).

Subjects underwent a physical exam, psychiatric and medical history, routine laboratory analyses, pregnancy test, electrocardiogram (ECG), assessment of vital signs, and administration of the MADRS (Montgomery and Asberg, 1979). Subjects were excluded if they had any serious unstable medical disorders, such as uncontrolled diabetes, hypertension, or seizures. Other exclusion criteria included pregnancy or breastfeeding, history of substance abuse within the past three months, any history of psychotic disorder, bipolar disorder, or current active suicidal ideation. Subjects who had previously failed to respond to escitalopram or pramipexole, or those treated with clozapine or electroconvulsive therapy (ECT) within three months prior to the study were also excluded. Patients were not permitted to participate in psychotherapy for the duration of the study. All subjects provided written informed consent as approved by the National Institutes of Health (NIH) Combined Neuroscience Institutional Review Board.

### 2.2. Study phases

This study comprised two phases. During Phase 1, subjects underwent a prospective trial of a standard antidepressant for six weeks at therapeutic doses and were required to be non-responsive to this agent, defined as not achieving 50% or greater improvement in MADRS scores from baseline. Subsequently, subjects meeting non-response criteria were gradually tapered off any psychotropic medications and were medication-free for 14 days (five weeks if the patient was taking fluoxetine). In the final week of the two-week, drug-free period, subjects received a single-blind placebo lead-in (Fig. 1). If there was a 25% or greater improvement in MADRS scores compared to study entry at the end of the single-blind

placebo week, or if the clinician judged a subject to be at acute risk of suicide, the subject was excluded and began standard treatment. All subjects were required to have a score of 20 on the MADRS at screening and at entry into Phase 2 of the study.

During Phase 2, subjects who met study criteria were randomized to six-week, double-blind treatment. Subjects were randomized to one of the following three groups: pramipexole; escitalopram; or a combination of pramipexole plus escitalopram. The blind was maintained with the use of a double-dummy design. Two types of capsules were used; one type contained pramipexole or its placebo and the other contained escitalopram or its placebo. Subjects assigned to the pramipexole group took pramipexole capsules and placebo-escitalopram capsules; the escitalopram group took escitalopram capsules and placebo-pramipexole capsules; and the combination group took escitalopram capsules and pramipexole capsules. All groups received the same number of pills.

Subjects taking pramipexole or the combination of both drugs received 0.375 mg/day of pramipexole during week 1 (0.125 mg three times per day (TID)). The pramipexole dose was subsequently increased in a blinded fashion as follows: week 2=0.25 mg TID, week 3=0.5 mg TID, week 4=0.75 mg TID. The maximum pramipexole dose was 0.75 mg TID (2.25 mg per day). Dose escalations of pramipexole were continued according to the above schedule until one of the following occurred: (1) clinical remission was achieved; (2) intolerable side effects occurred; (3) the maximum daily dose of pramipexole (2.25 mg/day) was achieved at week 4 or later; or (4) the six-week study period ended. The dose regimen of pramipexole used here was drawn from our previous study (Zarate et al., 2004). Subjects were assessed weekly throughout the study.

The initial power analysis suggested 24 patients per group (72 total) would be needed to have 80% power to detect a 35% increase in remission rates for the combination treatment compared to monotherapy. The study ended prior to reaching the full study size because interim results indicated that improved response to the combination treatment could not be shown even with a complete sample.

### 2.3. Measures

The MADRS was our primary outcome measure. The HDRS-17 (Hamilton, 1980) was also administered. To monitor side effects, the Massachusetts General Hospital Sexual Functioning Questionnaire (MGH) and the NIMH Event Codes were used. The former comprises five items evaluating interest, arousal, orgasm, erection, and overall sexual satisfaction (Labbate and Lare, 2001), and the latter is a clinician-administered assessment comprising 87 items that evaluate possible side effects on a scale from zero (none) to three (severe). Vital signs were collected, and rating scales were administered, at baseline and during each weekly visit until the end of the study.

### 2.4. Statistics

A linear mixed model with restricted maximum likelihood estimation was used to examine depressive symptoms and sexual side effects over time. Fixed factors for drug, time, and a time by drug interaction were included in the model along with the intercept. No random factors were included because the subject factor did not contribute significantly to the model. Baseline symptoms were used as a covariate. Schwarz's Bayesian criteria were used to determine the best fitting covariance structure that was a first order autoregressive model. Bonferroni adjusted simple effects tests were used post hoc to explore significant omnibus effects. Significance levels are reported after correction for post hoc analyses.

Chi-square analysis was used to examine categorical demographic variables, response rates, drop out, and general side effects by drug group. Continuous demographic factors were

examined with one-way ANOVAs and Tukey post hoc tests. Demographic and side effect comparisons were not adjusted for multiple comparisons.

Results were considered significant when  $p < 0.05$ , two tailed. IBM SPSS version 19.0 was used for all analyses.

### 3. Results

#### 3.1. Demographics

Fifty-eight subjects were screened (see Fig. 1), and 39 were randomized to blinded medication arms. Thirteen received pramipexole, 13 received escitalopram, and 13 received the combination of pramipexole plus escitalopram. Table 1 describes the demographic and clinical characteristics of the subjects; no statistically significant differences were observed between the three groups.

#### 3.2. Efficacy

Mean  $\pm$  SE MADRS scores for the three treatment groups over the six weeks of the study are presented in Fig. 2. The linear mixed model with MADRS as the outcome measure found significant drug and time main effects but no significant interaction (drug:  $F=4.45$ ,  $df=2,42$ ,  $p=0.02$ ; time:  $F=2.39$ ,  $df=5,133$ ,  $p=0.04$ ; drug  $\times$  Time:  $F=0.68$ ,  $df=10,133$ ,  $p=0.74$ ; Fig. 2). Baseline MADRS score was a significant covariate ( $F=7.88$ ,  $df=1,41$ ,  $p=0.008$ ). Post hoc tests indicated significantly lower MADRS scores with pramipexole compared to the combination treatment ( $p=0.01$ ), but no other comparisons were significant (pramipexole vs. escitalopram:  $p=0.35$ ; escitalopram vs. combination;  $p=0.45$ ).

Response was defined as 50% or better improvement at the six-week endpoint relative to baseline. Response rates were 31% (4/13) for subjects receiving pramipexole, 15% (2/13) for subjects receiving escitalopram, and 8% (1/13) for those receiving the combination treatment; no significant difference was noted in response rates ( $\chi^2=2.44$ ,  $df=2$ ,  $p=0.30$ ). Remission was defined as 75% improvement from baseline in MADRS scores as well as a final MADRS score of 9 or below. Remission rates for each group were 8% (1/13) for pramipexole, 15% (2/13) for escitalopram, and 0% (0/13) for the combination. No significant difference in remission rates was seen between the treatment groups ( $\chi^2=2.17$ ,  $df=2$ ,  $p=0.34$ ).

#### 3.3. Drop out

The dropout rate for the combination treatment group (9/13, 69%) was significantly higher than for the escitalopram (2/13, 15%) or pramipexole groups (2/13, 15%) ( $\chi^2=11.308$ ,  $df=2$ ,  $p=0.004$ ). On post hoc testing, the dropout rate remained significantly higher for the combination group than for either of the other two groups (vs. pramipexole:  $p=0.02$ ; vs. escitalopram:  $p=0.004$ ). In the pramipexole group, one patient was discontinued from the study due to worsening depression and another for shortness of breath and muscle spasms. In the escitalopram group one patient had worsening of depressive symptoms and one patient was non-compliant with medication. However, in the combination group, nine patients dropped out. One patient withdrew consent, one developed suicidal ideation, two experienced worsening mood, two were non-compliant with medication, and three had severe side effects (one had nausea and headaches, one had sleepiness and constipation, and one had tiredness, fatigue, and difficulty falling asleep).

#### 3.4. Sexual functioning

Linear mixed models were used to examine each of the five items of the MGH (Fig. 3). Main effects of drug were significant for lack of sexual interest ( $F=3.72$ ,  $df=2,29$ ,  $p=0.04$ ),

lack of sexual arousal ( $F=4.93$ ,  $df=2,32$ ,  $p=0.01$ ), inability to orgasm ( $F=4.52$ ,  $df=2,29$ ,  $p=0.02$ ), difficulty maintaining an erection ( $F=5.82$ ,  $df=2,9$ ,  $p=0.02$ ), and sexual dissatisfaction ( $F=9.03$ ,  $df=2,33$ ,  $p=0.001$ ). No significant interactions with time were observed (lack of sexual interest:  $F=0.91$ ,  $df=4,45$ ,  $p=0.47$ ; lack of sexual arousal:  $F=0.88$ ,  $df=4,49$ ,  $p=0.48$ ; inability to orgasm:  $F=1.57$ ,  $df=4,47$ ,  $p=0.20$ ; difficulty maintaining an erection:  $F=0.82$ ,  $df=4,14$ ,  $p=0.53$ ; sexual dissatisfaction:  $F=0.79$ ,  $df=4,49$ ,  $p=0.54$ ). Post hoc tests indicated significantly more symptoms in the combination group compared to the pramipexole group for all of the scales ( $p$ 's < 0.03) except lack of sexual interest, where there were only marginal group differences ( $p=0.053$ ). The combination group had significantly more sexual dissatisfaction than the escitalopram group ( $p=0.01$ ), but there were no significant differences with other symptoms ( $p$ 's > 0.59).

### 3.5. Side effects

Patients experiencing moderate or severe levels of a given side effect one or more weeks after randomization were coded as having experienced that side effect; a greater proportion of patients receiving escitalopram alone experienced sedation (55%) compared to patients receiving the combination treatment (0%) ( $p=0.009$ ). No other side effects evaluated were significantly different. No major changes in laboratory results or ECG were observed during the study.

For subjects in the pramipexole and combination groups, the pramipexole dose was raised in weekly increments starting at 0.375 mg/day and leading to 2.25 mg/day. Only 15% of the patients in the combination group were able to adhere to the regularly scheduled pramipexole increases throughout the study, compared to 46% of patients in the pramipexole monotherapy group. The mean dose ( $\pm$ SD) of pramipexole in the pramipexole monotherapy group vs. the combination group was 1.55 mg $\pm$ 0.56 vs. 1.16 mg $\pm$ 0.74, respectively; this difference was statistically marginal. Thus, the pramipexole monotherapy group was able to tolerate an almost 33% higher mean dose than the combination group.

## 4. Discussion

Contrary to our hypothesis, combining an SSRI and a dopamine agonist was not more effective than either agent alone, nor did it produce a more rapid onset of antidepressant action. Although six weeks of treatment with escitalopram had an antidepressant effect similar to that of pramipexole, this effect was not significantly different from the combination group. This lack of robust antidepressant effect from escitalopram, a proven antidepressant, could be attributed to the treatment resistance of the cohort or other factors.

This study also found that the dopamine agonist pramipexole had antidepressant effects; however, the fact that combining it with a serotonergic agent did not result in greater antidepressant effects raises questions as to whether combining serotonergic agents with dopamine agonists is a dual mechanism worth pursuing, largely because of intolerability issues. One possibility for the lack of significant findings could have been that the combination therapy group had a greater number of intolerable side effects than either monotherapy group, leading to greater drop-out rates. Indeed, it is important to note that most patients in the combination group dropped out complaining of severe side effects. In contrast, no patients in the escitalopram monotherapy group dropped out (Fig. 1) despite the comparatively higher rate of sedation in that group. However, we cannot determine how the combination group side effect profile would have evolved if they had remained in the study.

A non-tolerability factor associated with the combination of escitalopram and pramipexole remains a likely possibility, as shown by the number of patients in the combination group who were not able to tolerate increases in the total daily dose of pramipexole when

compared to subjects receiving pramipexole alone. Several open and controlled studies have used pramipexole as an augmentation strategy to treat patients, but in most studies pramipexole was added to an antidepressant or mood stabilizer after that agent was already being administered at therapeutic doses (Goldberg et al., 2004; Inoue et al., 2010; Lattanzi et al., 2002; Sporn et al., 2000; Zarate et al., 2004). In our study both escitalopram and pramipexole treatment were started at the same time; it is possible that the simultaneous activation of both the serotonergic and dopaminergic systems contributed to the high dropout rates from the combination group. Considering the evidence of low initiation of selected treatments and low adherence to them (Serna et al., 2010), it is important to understand the implications of these findings in order to avoid iatrogenic treatment discontinuation.

The symptom improvement observed in the pramipexole group is consistent with the notion that the dopaminergic system plays a role in treating MDD (Guiard et al., 2009; Yadid and Friedman, 2008). Nevertheless, the fact that combination therapy did not improve depressive symptoms and showed poor tolerability calls into question the interaction between the serotonergic and dopaminergic systems in the brain. It may be the case that agonism of dopamine receptors might be an effective augmentation strategy but only after the serotonergic system has been stabilized with a serotonergic agent.

Another interesting finding was that pramipexole monotherapy was associated with significantly fewer sexual side effects than escitalopram monotherapy; no such protective effect against sexual side effects was seen in the combination group. Indeed, the favorable sexual side effect profile was only seen in patients receiving pramipexole monotherapy, not when this medication was used in combination with escitalopram. In addition, the high dropout rate in the combination group did not seem to be due to the increased incidence of sexual adverse events.

The study was associated with several limitations and, as a result, the results must be interpreted with caution. Most notably, group size was small and the treatment phase lasted for only six weeks. More time may be required to observe greater response in the monotherapy groups.

In conclusion, this preliminary study investigated combined treatment with an SSRI and a dopamine agonist in patients with MDD and found that this combination was not well tolerated and did not lead to increased efficacy. Our findings emphasize the need to better understand the role of the simultaneous activation of the serotonergic and dopaminergic systems in order to develop more effective combination strategies for treating MDD. Larger and longer controlled studies are clearly warranted to better assess the treatment role of dopamine agonists in MDD.

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The NIMH had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Dr. Zarate is listed as a co-inventor on a patent application for the use of ketamine and its metabolites in major depression. Dr. Zarate has assigned his rights in the patent to the U.S. Government but will share a percentage of any royalties that may be received by the Government. This work was initiated at the NIMH prior to Dr. Mallinger's official duties with the Office of the Inspector General. The views expressed in this paper do not

necessarily represent the views of the Office of Inspector General, the Department of Veterans Affairs, or the United States Government.

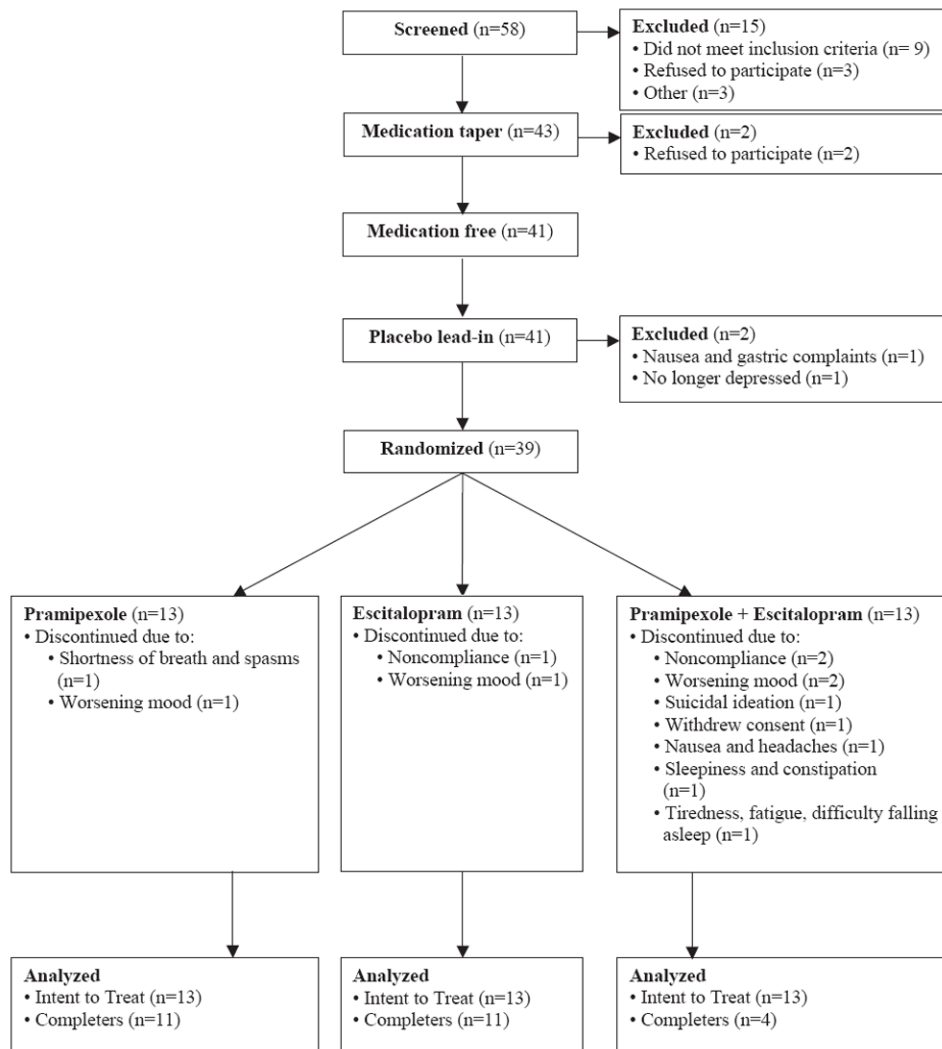
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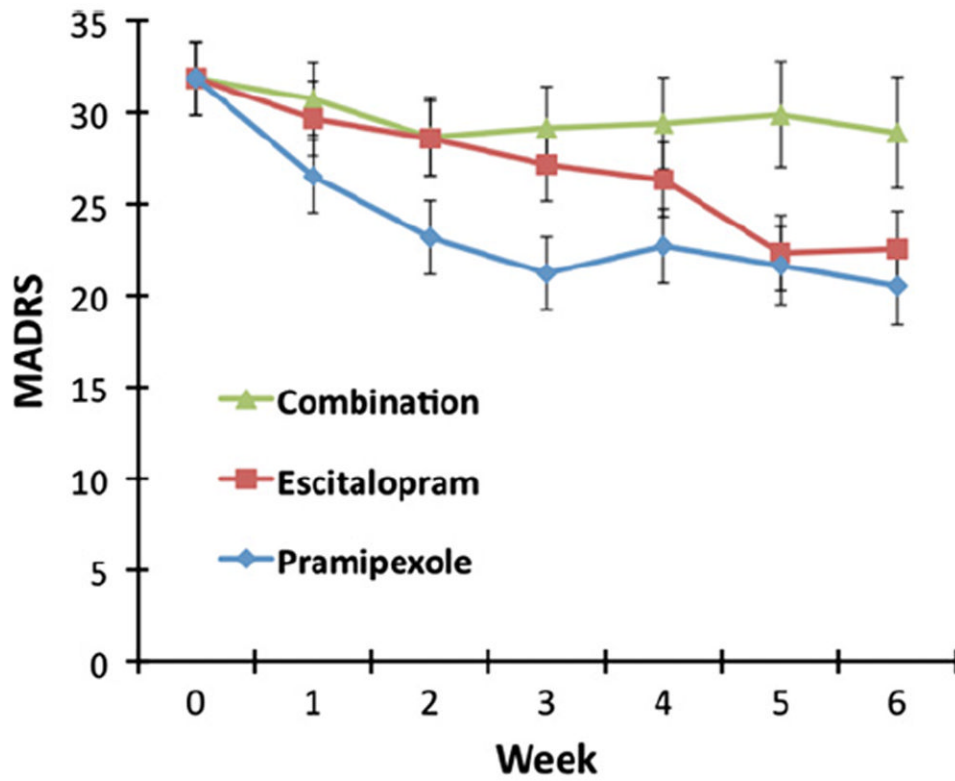


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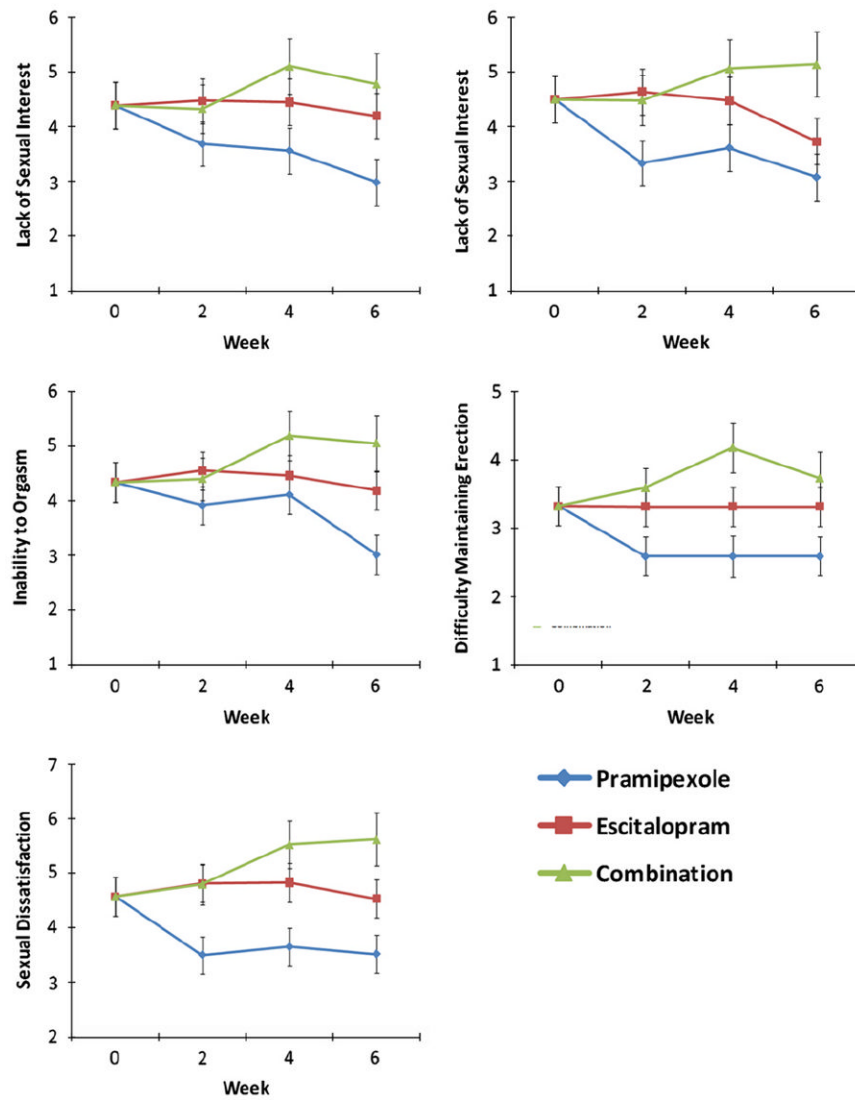
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**Fig. 1.** CONSORT diagram indicating patient recruitment, exclusion, and randomization.



**Fig. 2.** Mean depression score on the Montgomery Asberg Depression Rating Scale (MADRS) over six weeks. Linear mixed models using MADRS score as the outcome produced significant drug and time main effects ( $F=4.45$ ,  $df=2,42$ ,  $p=0.02$  and  $F=2.39$ ,  $df=5,122$ ,  $p=0.04$ , respectively).



**Fig. 3.** Mean score for each of the five items of the Massachusetts General Hospital Sexual Functioning Questionnaire across six visits. Linear mixed models produced significant main effects of drug for all items: sexual interest ( $F=3.72$ ,  $df=2,29$ ,  $p=0.04$ ), lack of sexual arousal ( $F=4.93$ ,  $df=2,32$ ,  $p=0.01$ ), inability to orgasm ( $F=4.52$ ,  $df=2,29$ ,  $p=0.02$ ), difficulty maintaining an erection ( $F=5.82$ ,  $df=2,9$ ,  $p=0.02$ ), and sexual dissatisfaction ( $F=9.03$ ,  $df=2,33$ ,  $p=0.001$ ).

**Table 1**

Demographic and illness characteristics for patients receiving pramipexole, escitalopram, or pramipexole plus escitalopram.

Sample Characteristics	Pramipexole (n=3) N (%)	Escitalopram (n=13) N (%)	Combination (n=13) N (%)	$\chi^2, p$
Sex (female)	7 (54)	9 (69)	10 (77)	1.62, 0.45
Ethnicity				2.82, 0.59
• Caucasian	5 (38)	9 (69)	6 (46)	
• Black	3 (23)	2 (17)	3 (25)	
• Hispanic	5 (38)	2 (17)	4 (33)	
Co-morbidity				
• Anxiety disorders	5 (38)	7 (58)	7 (58)	0.82, 0.66
• Lifetime substance abuse or dependence	4 (31)	4 (31)	4 (31)	0.00, 1.00
	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>F, p</b>
Age	44.9 (10.1)	45.6 (13.6)	46.1 (12.5)	0.04, 0.96
Age of onset	24.3 (11.0)	19.6 (10.2)	27.1 (16.3)	1.14, 0.33
Duration of current episode (months)	21.9 (30.0)	34.3 (65.1)	19.8 (24.8)	0.42, 0.66
Lifetime antidepressant trials	1.92(1.12)	2.54(1.39)	1.83(1.03)	1.32, 0.28
Failed antidepressant trials	1.45(1.13)	2.00(1.28)	1.36(0.51)	1.28, 0.29
Baseline				
• MADRS	33.5 (4.8)	30.1 (5.4)	31.4 (5.6)	0.70, 0.50
• HDRS-17	20.1 (5.1)	18.0 (3.8)	21.0 (5.0)	1.00, 0.37

Abbreviations: MADRS, Montgomery Asberg Depression Rating Scale; HDRS-17, 17-Item Hamilton Depression Rating Scale.