A Randomized, Double-Blind, Placebo-Controlled Trial of Pramipexole Augmentation in Treatment-Resistant Major Depressive Disorder

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ABSTRACT

Background: Multiple treatments for patients with major depressive disorder (MDD) have demonstrated efficacy, but up to one-third of individuals with MDD do not achieve symptomatic remission despite various interventions. Existing augmentation or combination strategies can have substantial safety concerns that may limit their application.

Method: This study investigated the antidepressant efficacy of a flexible dose of the dopamine agonist pramipexole as an adjunct to standard antidepressant treatment in an 8-week, randomized, double-blind, placebo-controlled trial conducted in a tertiary-level depression center. We randomized 60 outpatients (aged 18 to 75 years) with treatment-resistant nonpsychotic MDD (diagnosed according to *DSM-IV*) to either pramipexole (n = 30) or placebo (n = 30). Treatment resistance was defined as continued depression (Montgomery-Asberg Depression Rating Scale [MADRS] score ≥ 18) despite treatment with at least 1 prior antidepressant in the current depressive episode. Patients were recruited between September 2005 and April 2008. The primary outcome measure was the MADRS score.

Results: The analyses that used a mixed-effects linear regression model indicated a modest but statistically significant benefit for pramipexole ($P = .038$). The last-observation-carried-forward analyses indicated that 40% and 33% of patients randomized to augmentation with pramipexole achieved response ($\chi^2 = 1.2$, $P = .27$) and remission ($\chi^2 = 0.74$, $P = .61$), respectively, compared to 27% and 23% with placebo; however, those differences were not statistically significant. Augmentation with pramipexole was well-tolerated, with no serious adverse effects identified.

Conclusion: For patients who have failed to respond to standard antidepressant therapies, pramipexole is a safe and potentially efficacious augmentation strategy.

Trial Registration: ClinicalTrials.gov identifier: NCT00231959

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Multiple treatments for patients with major depressive disorder (MDD) have demonstrated efficacy, but up to one-third of patients with MDD fail to achieve symptomatic remission with an antidepressant trial.[1] While multiple augmentation strategies have demonstrated efficacy versus placebo, in some cases, the utility of these strategies remains limited by concerns about long-term safety and tolerability. In particular, concerns have been raised regarding augmentation with atypical antipsychotics such as olanzapine, quetiapine, and aripiprazole.[2–5] This divergence of opinions about the use of atypical antipsychotics as augmentation treatment in MDD is reflected in current treatment guidelines.[6] Therefore, the need for identification of safe and effective treatments for patients who fail to respond to antidepressants remains acute. One possible treatment strategy relies on drugs such as bupropion[7] and psychostimulants[8] thought to modulate the dopaminergic system, a pathway that has been implicated in depressive symptoms such as psychomotor retardation and anhedonia[9] and that may be implicated in response to different antidepressant treatments.[10–13]

Pramipexole is an amino-benzothiazole dopamine receptor agonist that is approved by the US Food and Drug Administration (FDA) as monotherapy or adjunctive therapy for idiopathic Parkinson's disease and for restless leg syndrome. Pramipexole has high in vitro specificity for the D_2 subfamily of dopamine receptors; it is a full agonist and has greater affinity for the D_3 receptor subtype than for the D_2 or D_4 receptor subtypes.[14,15]

Preclinical and early clinical data[16–18] suggested that pramipexole may have antidepressant effects. An initial report from our group[19] described significant improvement in a case series of 32 patients with MDD or bipolar depressive episode treated with pramipexole augmentation therapy. In 4 open-label studies,[20–23] the authors reported a significant decline in depression severity scores with pramipexole augmentation of antidepressants. The largest study[24] of pramipexole in depression included 174 patients with MDD. In that study, patients were randomized to 5 arms, consisting of 3 different daily doses of pramipexole monotherapy (0.375 mg, 1.0 mg, or 5.0 mg), fluoxetine 20 mg, or placebo. Patients treated with pramipexole 1.0 mg/d or fluoxetine showed significant improvement in depression severity scores compared to those taking placebo, and the efficacy of the 2 drugs appeared similar, but no direct comparison between fluoxetine and pramipexole was reported.

Other preliminary reports[9,25] have also suggested efficacy for pramipexole in bipolar depression. Whether pramipexole represents a useful augmentation strategy, however, has not been investigated in randomized trials. We therefore examined the efficacy and

Clinical Points

- For patients who have failed to respond to standard antidepressant therapies, pramipexole is a safe and potentially efficacious augmentation strategy.
- Augmentation with pramipexole was well tolerated at a mean (SD) dose of 1.35 (0.31) mg/d.

safety of pramipexole augmentation of antidepressants in a randomized, double-blind, placebo-controlled trial in patients with treatment-resistant depression.

METHOD

Subjects

Eligible outpatients were recruited (between September 2005 and April 2008) at the Depression Clinical and Research Program at Massachusetts General Hospital in Boston. Inclusion criteria were age between 18 and 75 years and meeting *DSM-IV* diagnostic criteria for current nonpsychotic MDD, with a Montgomery-Asberg Depression Rating Scale (MADRS)[26] score ≥ 18. In addition, patients were required to have completed at least 1 prior antidepressant intervention of adequate dose and duration during the current episode. If treatment resistance could not clearly be established by clinical interview and record review, individuals would enter an open selective serotonin reuptake inhibitor (SSRI) lead-in phase for 6 weeks to ensure 6 weeks of antidepressant treatment at adequate dose, according to specific predefined criteria (later validated in the Massachusetts General Hospital Antidepressant Treatment History Questionnaire[27]). To maximize homogeneity of treatment groups, only patients who had had treatment failure with an SSRI or a serotonin-norepinephrine reuptake inhibitor (SNRI; venlafaxine or duloxetine) were enrolled in this study. Individuals with a concurrent diagnosis of any anxiety disorder were not excluded, provided they also met criteria for a current major depressive episode, in order to increase the generalizability of our findings.

Exclusion criteria were any diagnosis of bipolar disorder, untreated or unstable general medical illness (including uncontrolled seizure disorder), substance use disorder active within the last 6 months or a positive urine drug screen, diagnosis of Parkinson's disease, lifetime history of psychotic features as assessed by the Structured Clinical Interview for *DSM-IV* Axis I Disorders,[28] serious suicide or homicide risk requiring acute intervention, current treatment with an antipsychotic medication, current treatment with any medication known to significantly interact with pramipexole metabolism (eg, cimetidine, kava), pregnancy or being of child-bearing potential and not using a medically accepted means of contraception, prior 2-week or greater course of pramipexole, intolerance of pramipexole at any dose, or use of any investigational psychotropic drug within the last 3 months. All patients provided written informed consent to participate in the study protocol, which was approved by the institutional review board of the Massachusetts General Hospital, Boston. The study was registered on ClinicalTrials.gov (identifier: NCT00231959).

Study Design

Following the screening and the baseline assessment, patients continued for 6 weeks with their antidepressant treatment, when necessary, to confirm treatment resistance, with visits every 2 weeks. The eligible patients who continued to meet inclusion criteria for the study were randomized to double-blind, add-on, flexibly dosed pramipexole or placebo for 8 weeks. The randomization was stratified by duration of current episode (< 2 years or ≥ 2 years) and study entry path (immediate randomization vs open-label lead-in) to ensure that these strata were equally represented across the 2 treatment arms. Flexible dosing was chosen because it allows the dose to be adjusted and optimized for each patient, which more closely reflects clinical practice with antidepressants. The guidelines for the study clinicians recommended a pramipexole starting dose of 0.25 mg twice per day (bid), with an increase to 0.50 mg bid at week 1, 0.75 mg bid at week 2, and 1.00 mg bid at week 3. The target dosage was 1.50 mg bid when tolerated.

During this 8-week study, patients were assessed weekly for the first 4 visits and then every other week until completion. The primary efficacy measure was the MADRS. Remission was defined a priori as a MADRS score ≤ 10 at study end point, while response was defined as 50% improvement compared to baseline.

Secondary measures of efficacy included change in the Clinical Global Impressions-Severity of Illness scale (CGI-S)[29] score and change in the 30-item Inventory of Depressive Symptomatology Self-Rated version (IDS-SR)[30,31] score over 8 weeks. Subjects who experienced a significant worsening of depression, defined as a CGI-Improvement (CGI-I)[29] score of 6 (much worse) or 7 (very much worse) at any point in the trial were dropped from the protocol and were offered 3 months of free follow-up care.

Data Analysis

Safety analyses were conducted on all enrolled patients, while efficacy analyses were conducted on all patients who completed at least 1 week of treatment (modified intent-to-treat cohort). Primary analyses utilized mixed-effects models as well as more conservative last-observation-carried-forward (LOCF) analyses. Mixed-effects models enable more efficient use of data, as they incorporate repeated measures and allow the inclusion of data from subjects who have mistimed or missing data. This approach has been suggested to offer substantial advantages over traditional LOCF methods.[32] Power was conservatively estimated using an unpaired *t* test. With 30 subjects randomized, power was greater than 76% to detect effect sizes greater than 0.7. The actual power is substantially greater than 80% because of the availability of repeated measures for mixed-effects analysis.

Table 1. Baseline Demographic and Clinical Characteristics and End Point Scores for Patients Randomized to Pramipexole or Placebo (N = 60)

Characteristic	Placebo Group (n = 30)	Pramipexole Group (n = 30)	Statistic	*P* Value
Gender, male, %	40.0	46.7	$\chi^2 = 0.27$	.60
Chronic MDD, %	56.7	40.0	$\chi^2 = 1.67$	.20
SNRI (vs SSRI), n (%)	8 (26.7)	5 (16.7)	$\chi^2 = 0.88$	.35
Prospective lead-in, n (%)	5 (16.7)	5 (16.7)	$\chi^2 = 0.00$	1.0
Age, mean (SD), y	45.5 (1.8)	47.3 (12.9)	$t = -0.056$	.57
Age at onset, mean (SD), y	20.9 (10.2)	25.0 (15.4)	$t = -1.13$	.26
Lifetime number of episodes, mean (SD)	3.2 (2.9)	3.5 (3.3)	$t = -0.28$	.78
Number of previous trials, mean (SD)	2.0 (1.0)	1.9 (1.0)	$t = 0.63$	.53
Duration of current episode, mean (SD), wk	47.3 (52.2)	36.9 (52.6)	$t = 0.65$	.52
MADRS baseline score, mean (SD)	27.2 (5.8)	27.4 (5.9)	$t = -0.11$	.91
CGI baseline score, mean (SD)	4.3 (0.6)	4.3 (0.6)	$t = 0.41$	.69
IDS-SR baseline score, mean (SD)	39.4 (12.0)	35.9 (10.7)	$t = 1.18$	.38
MADRS end point score, mean SD	20.5 (11.7)	18.0 (10.4)	$t = 0.89$	.47
CGI end point score, mean (SD)	3.5 (1.4)	3.0 (1.5)	$t = 1.24$	.34
IDS-SR end point score, mean (SD)	33.8 (14.8)	29.4 (12.0)	$t = 1.27$	.33

Abbreviations: CGI = Clinical Global Impressions scale, IDS-SR = Inventory of Depressive Symptomatology-Self-Rated, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, SD = standard deviation, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

RESULTS

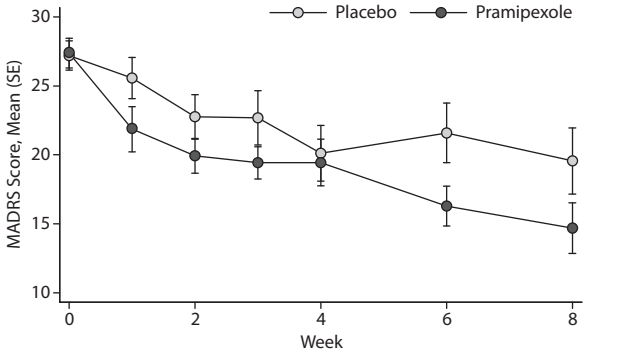
A total of 86 subjects were recruited, of whom 60 were randomized and included in the modified intent-to-treat analyses. No significant baseline differences in sociodemographic and clinical features were observed between randomization groups (Table 1). Among placebo-treated patients, the primary antidepressants were duloxetine (n = 2), venlafaxine (n = 6), escitalopram (n = 10), fluoxetine (n = 4), sertraline (n = 7), and citalopram (n = 1). Among pramipexole-treated patients, the primary antidepressants were duloxetine (n = 1), venlafaxine (n = 4), escitalopram (n = 12), paroxetine (n = 1), fluoxetine (n = 4), and sertraline (n = 8). Twenty-one enrolled subjects had experienced 1 prior antidepressant treatment failure, 19 had experienced 2 prior antidepressant treatment failures, and 20 had experienced failure of 3 or more prior antidepressant trials. Ten patients participated in the lead-in phase, 5 of whom were randomized to the pramipexole group and 5 to the placebo group.

Efficacy

Among 60 randomized subjects in the modified intent-to-treat cohort, 42 completed 8 weeks of treatment (20 in the placebo group, 22 in the pramipexole group; $\chi^2 = 0.57$, $P = .55$); the median number of postbaseline visits was 6 for both groups. The primary analysis applied mixed-effects linear regression. The secondary analyses included the variables decided on a priori as covariates: lead-in status, primary antidepressant, number of past treatment trials, age, sex, and baseline MADRS severity.

The results indicated a modest but statistically significant time effect favoring pramipexole ($\beta = -1.89$, standard error [SE] = 0.91; $z = -2.08$, $P = .038$). Figure 1 shows the change in MADRS scores over time, using mixed-effects linear regression analyses. At end point, LOCF analyses indicated that the mean decrease in MADRS scores was 9.4 for the pramipexole group, versus 6.7 for the placebo group (Student $t = -1.15$, $P = .23$). Similar models were fit for the self-report outcome, the IDS-SR, which was completed at each visit. The difference between groups on the IDS-SR was not statistically significant ($\beta = -1.70$, SE = 1.02; $P = .09$). The LOCF analyses indicated mean change scores for the IDS-SR of 6.5 points for the pramipexole group and 4.0 points for placebo group. However, the difference between these groups on IDS-SR scores was not statistically significant.

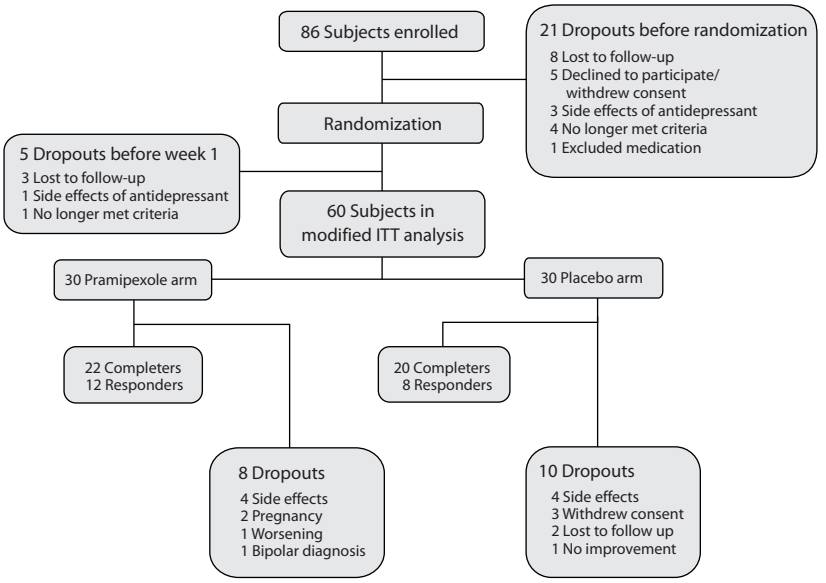
Figure 1. Mixed-Effects Linear Regression Analysis of Montgomery-Asberg Depression Rating Scale (MADRS) Scores Over Time, by Treatment Group



For descriptive purposes, we also estimated the proportion of subjects who had achieved response and remission at end point. For response, 12 of 30 pramipexole-treated subjects (40.0%) and 8 of 30 placebo-treated subjects (26.7%) met the response criteria at end point ($\chi^2 = 1.2$, $P = .27$). For remission, 10 of 30 pramipexole-treated subjects (33.3%) and 7 of 30 placebo-treated subjects (23.3%) achieved remission at end point ($\chi^2 = 0.74$, $P = .61$).

To perform exploratory analyses of moderators, we used mixed-effects linear regression analyses to investigate

Figure 2. Flow Diagram of Study Subjects



Abbreviation: ITT = intent-to-treat.

improvement in MADRS scores in subjects who had had treatment failure with 1 prior antidepressant ($\beta = -0.43$, SE = 2.13; $P = .84$) and in those who had had treatment failure with 2 or more antidepressants ($\beta = -1.92$, SE = 1.01; $P = .06$). The trend toward significant improvement among those patients who had experienced treatment failure with 2 or more trials indicates a possible increased benefit of pramipexole in subjects who have previously had 2 or more failed treatments. Concomitant antidepressant class also demonstrated a moderating effect that trended toward significance, such that there was increased benefit for pramipexole in patients taking an SNRI ($\beta = -0.43$, SE = 2.64) compared with patients taking an SSRI ($\beta = -1.35$, SE = 1.06), although the sample size was small and the difference did not reach statistical significance.

Tolerability

The mean (standard deviation [SD]) daily dose of pramipexole at the end of the trial was 1.35 (0.31) mg. Among the randomized patients, 18 (30%) did not complete the study; the reasons for discontinuation are presented in Figure 2. Four patients in each group withdrew because of side effects, 2 patients randomized to pramipexole withdrew due to pregnancy, and 2 patients in the pramipexole group experienced worsening of symptoms. In the placebo group, 3 subjects withdrew consent, and 2 were lost to follow-up. One patient (assigned to pramipexole) revealed additional history at week 1 that raised substantial clinician concern about bipolar disorder, and that patient was discontinued from the study.

During the course of the study, no serious adverse events were observed. One subject in the pramipexole group experienced a clinically significant worsening (CGI-I = 6) that was determined not to be drug-related but was related to an ongoing medical condition; per protocol, the subject was discontinued from the study. Mild and moderate side effects are reported in Table 2; no severe side effects were reported. The most commonly reported side effects were xerostomia, perspiration, difficulty in coordination, constipation, urinary frequency, malaise, and restlessness, which were not significantly different between drug and placebo. Three nominally significant differences were observed between treatment groups. In patients receiving pramipexole, constipation was reported more frequently; conversely, pramipexole-treated patients reported significantly less itching and less impairment in sexual desire and orgasm compared to patients receiving placebo.

DISCUSSION

The present study is, to our knowledge, the first randomized, double-blind, placebo-controlled trial evaluating the efficacy, safety, and tolerability of pramipexole as adjunctive therapy for patients with MDD who were nonresponders to 1 or more trials of monotherapy with an SSRI or SNRI. On average, mixed-effects models suggest a modest but statistically significant benefit with pramipexole. Using more traditional LOCF analyses of response and remission rates, similar differences were detected in MADRS scores, but these differences did not reach statistical significance. In this study, the augmentation with pramipexole was well tolerated, with no serious adverse effects at a mean (SD) daily dose of 1.35 (0.31) mg. The incidence of mild to moderate side effects was comparable for pramipexole and placebo, and pramipexole was not associated with higher discontinuation rates. Notably, the significantly decreased incidence of sexual side effects in patients treated with pramipexole may indicate a possible benefit of pramipexole as adjunctive therapy in patients experiencing adverse effects with SSRIs or SNRIs,

Table 2. Treatment-Emergent Adverse Events in Either Treatment Group During the Randomized, Double-Blind Treatment Phase (N = 60)

Adverse Event	Placebo Group (n = 30), n	Pramipexole Group (n = 30), n	χ^2	*P* Value[a]
Difficulty sleeping	6	5	0.182	.67
Xerostomia	10	11	0.080	.78
Palpitations	8	8	0.053	.82
Dizziness on standing	9	9	0.008	.93
Perspiration	9	10	0.000	.99
Dry skin	11	7	0.935	.33
Headaches	9	8	0.032	.86
Difficulty in coordination	10	9	0.236	.63
Diarrhea	5	6	0.171	.68
Constipation	3	12	9.256	**.001**
Chest pain	4	2	0.814	.37
Rash	4	3	0.201	.65
Itching	8	1	6.533	**.01**
Tremors	6	9	1.517	.22
Dizziness	7	11	0.606	.44
Blurred vision	8	8	0.007	.93
Tinnitus	6	4	0.331	.56
Difficulty urinating	3	3	0.007	.93
Painful urination	1	0	1.084	.30
Increased urinary frequency	6	11	1.623	.20
Menstrual irregularity	4	2	0.601	.44
Hypersomnia	5	7	0.458	.50
Loss of sexual desire	6	1	4.887	**.03**
Difficulty with orgasm	7	6	1.325	.25
Difficulty with erection	4	3	0.166	.68
Anxiety	6	7	0.906	.34
Concentration	4	6	0.220	.64
Malaise	11	8	2.030	.15
Restlessness	10	10	0.000	1.0
Fatigue	6	6	0.048	.83
Decreased energy	5	7	2.253	.13
Nausea or vomiting	7	13	2.176	.14

[a]Bolded *P* values indicate nominal significance at $P < .05$.

although this finding may also represent a type I error in light of the number of adverse effects compared.

Overall, these results support the hypothesis that, for patients with an incomplete response to 1 or more antidepressant therapies, pramipexole is a safe and potentially useful augmentation strategy.

A strength of the study is the rigorous definition of treatment nonresponse (equivalent to a level of treatment resistance of 1 or 2 according to the classification of Thase and Rush[33]), as patients who did not have a clear history of treatment resistance underwent a prospective 6-week lead-in phase prior to randomization. Conversely, a primary limitation of the study was the modest power to detect smaller treatment effects, necessitated by the single-site design and stringent entry criteria. To improve generalizability and feasibility, subjects could enter the study while taking either an SSRI or an SNRI, and 1 or more prior treatment failures were allowed. It is also possible that heterogeneity in the level of treatment resistance could have obscured larger drug effects in a patient subset. Another limitation of the study is related to the relatively high dropout rate in both active treatment and placebo conditions. As suggested in a recent article,[34] dropouts can be nonrandomly distributed, and it is possible that early dropouts in the drug arm could be related to side effects, while late dropouts in the placebo arm could be related to lack of improvement. However, the number of subjects who discontinued the study after randomization because of side effects was not different between the placebo and pramipexole groups. Regarding the 2 pregnancies that caused dropouts in the pramipexole arm, we cannot exclude that those were related to an increase in impulsivity, although both patients were young married women and one of them had been trying to conceive for years.

Notwithstanding these limitations, the results of this study provide some support for the efficacy of adjunctive pramipexole as an augmentation of SSRIs or SNRIs in patients with a history of nonresponse or partial response to antidepressants. Given the substantial number of patients who do not achieve remission with initial antidepressant treatment, and given the substantial safety concerns about the atypical antipsychotics presently approved by the FDA for this indication, the suggestion that an alternate strategy with adjunctive pramipexole may have utility merits further investigation.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin, Aplenzin, and others), cimetidine (Tagamet and others), citalopram (Celexa and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), olanzapine (Zyprexa and others), paroxetine (Paxil, Pexeva, and others), pramipexole (Mirapex and others), quetiapine (Seroquel and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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Potential conflicts of interest: **Dr Iosifescu** has been a consultant for CNS Response, Forest, Gerson Lehrman, and Pfizer; has received grant support from Aspect Medical Systems, Forest, Janssen, NARSAD, and the National Institutes of Health; and has received speaker honoraria from Eli Lilly, Forest, Pfizer, and Reed Elsevier (a company working as logistics collaborator for the Massachusetts General Hospital (MGH) Psychiatry Academy; education programs conducted by the Academy were supported through independent medical education grants from pharmaceutical companies co-supporting programs along with participant tuition). **Dr Nierenberg** has consulted for the American Psychiatric Association (only travel expenses were paid), Appliance Computing (Mindsite), AstraZeneca, Basilea, BrainCells, Brandeis University, Bristol-Myers Squibb, Dainippon Sumitomo/Sepracor, Eli Lilly, EpiQ, Johnson & Johnson, Labopharm, Merck, Methylation Science, Novartis, PGx Health, Shire, Schering-Plough, Takeda/Lundbeck, and Targacept; has received grant/research support through MGH from the National Institute of Mental Health (NIMH), Pamlabs, Pfizer, and Shire; has received honoraria from Belvoir Publishing, University of Texas Southwestern Dallas, Hillside Hospital, American Drug Utilization Review, American Society for Clinical Psychopharmacology, Baystate Medical Center, Columbia University, Imedex, MJ Consulting, New York State, Medscape, MBL Publishing, Physicians Postgraduate Press, State University of New York at Buffalo, University of Wisconsin, University of Pisa, American Professional Society of ADHD and Related Disorders, International Standard Bibliographic Description, and SciMed; has been a presenter for the MGH Psychiatry Academy (education programs conducted by the Academy were supported through independent medical education grants from various pharmaceutical companies). **Dr Fava** has received research support from Abbott, Alkermes, Aspect Medical Systems, AstraZeneca, BioResearch, BrainCells, Bristol-Myers Squibb, CeNeRx, Cephalon, Clintara, Covance, Covidien, Eli Lilly, ElMindA, EnVivo, Euthymics Bioscience, Forest, Ganeden, GlaxoSmithKline, Icon Clinical Research, i3 Innovus/Ingenix, Johnson & Johnson PRD, Lichtwer, Lorex, NARSAD, the National Center for Complementary and Alternative Medicine, the National Institute on Drug Abuse, NIMH, Novartis, Organon, Pamlab, Pfizer, Pharmavite, Photothera, Roche, RCT Logic (formerly Clinical Trials Solutions), Sanofi-Aventis, Shire, Solvay, Synthelabo, and Wyeth-Ayerst; has served as an advisor/consultant for Abbott, Affectis, Alkermes,

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