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Antidepressant Studies in Parkinson's Disease:

A Review and Meta-Analysis

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Abstract

The objective of this study was to determine effect sizes for both antidepressant treatment and placebo for depression in Parkinson's disease (PD), and to compare the findings with those reported in elderly depressed patients without PD. Recent reviews have concluded that there is little empiric evidence to support the use of antidepressants in PD; however, available data has not been analyzed to determine the effect size for antidepressant treatment in PD depression. A literature review identified antidepressant studies in PD. Suitable studies were analyzed using meta-analytic techniques, and effect sizes were compared with those from antidepressant studies in elderly patients without PD. Large effect sizes were found for both active treatment and placebo in PD, but there was no difference between the two groups. In contrast, active treatment was superior to placebo in depressed elderly patients without PD. In PD, increasing age and a diagnosis of major depression were associated with better treatment response. Results also suggest that newer antidepressants are well tolerated in PD. Despite the high prevalence of depression and antidepressant use in PD, controlled treatment research has been almost non-existent. Meta-analysis results suggest a large but nonspecific effect for depression treatment in PD. In addition, PD patients may benefit less from antidepressant treatment, particularly selective serotonin reuptake inhibitors, than do elderly patients without PD.

Keywords

Parkinson's disease; depression; antidepressive agent; treatment; effect size; meta-analysis

It is estimated that 30 to 40% of patients with Parkinson's disease (PD) suffer from some form of depression[1,2] and 20 to 25% of patients receiving specialty care are taking an antidepressant.[3,4] Despite the high prevalence of depression and antidepressant use in PD, many questions remain concerning the diagnosis and treatment of depression in this population. For instance, accurately diagnosing depression in PD can be difficult, as there is symptom overlap between core PD and depression symptoms (e.g., psychomotor changes, fatigue, insomnia, and apathy).

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In addition, recent research suggests that most cases of depression in PD may represent episodes of minor or recurrent brief depression[1,5] calling into question the usefulness of antidepressant treatment for many PD patients with depression.

Although there is an extensive literature on the epidemiology and phenomenology of depression in PD,[6-12] there have been relatively few treatment studies. In the psychosocial realm, a small pilot study suggested that cognitive psychotherapy might be helpful for depression in PD,[13] but there have been no controlled studies of psychosocial treatments.

Concerning antidepressant treatment in PD, almost all existing studies have been either uncontrolled (i.e., open-label) or underpowered placebo-controlled studies.[5,14] The use of open-label studies is particularly problematic in PD, as a high placebo response rate has been reported in this population.[15] In addition, a key outcome measure is the impact of antidepressant treatment on parkinsonism, which is best assessed in a blinded, placebo-controlled trial.

A 1995 review (covering 1966 to June 1993) of published studies identified only 12 depression treatment studies in PD, 4 of which were thought to have adequate methodology.[16] The authors concluded, “The main conclusion to be drawn from this review is that presently there is no empirical evidence on which to base a treatment plan for depression in patients with Parkinson’s disease.” A 2002 review (years covered in review not specified) of depression treatment in PD identified 19 antidepressant studies, only 5 of which were thought suitable for inclusion in the review.[17] Regarding newer antidepressants, the authors stated, “There is insufficient evidence available to conclude on the efficacy of SSRIs as a class for treatment of depression in patients with Parkinson’s disease.” Finally, a 2003 Cochrane Database review (covering 1800s to February 23, 2001) of antidepressant therapies for depression in PD identified three randomized controlled trials of oral antidepressant medications and concluded, “Insufficient data on the effectiveness and safety on any antidepressants therapies in Parkinson’s disease are available on which to make recommendations for their use.”[18]

The aforementioned reviews used different criteria to rate the quality of individual studies and did not attempt to analyze statistically the available data to determine the effect of antidepressant treatment. To assess the impact of antidepressant treatment in PD, we reviewed the English language literature on depression in PD and employed meta-analytic procedures, incorporating the effect size of each study as the unit of analysis to examine the influences of pharmacologic treatment on depression in PD. Effect size is defined as the magnitude of the mean difference between pre- and post-assessment measures, expressed in standard deviation units.[19] In the current meta-analysis, the primary effect size examined was the difference between pre- and posttreatment scores on depression rating scales in depressed PD patients.

The aims of this meta-analysis were to examine the difference between active and placebo treatment on depression in PD, to compare these findings to treatment studies involving elderly depressed patients without PD, and to probe for moderators of antidepressant treatment response in PD.

MATERIALS AND METHODS

Literature Search

A literature review (1 January 1965 to 31 December 2003) of English-language studies concerning the treatment of depression and the use of antidepressants in PD was conducted on July 1, 2003 and January 1, 2004 using online databases (Medline, PubMed, and PsycINFO) and reference lists from reviewed articles. Primary search terms were *Parkinson’s disease, depression, antidepressive agents*, and *therapy*.

To be included in the general review, a study had to enroll subjects with parkinsonism, use a medication with reported antidepressant effects, and report the outcome of antidepressant treatment. Levodopa (L-dopa) and dopamine agonists were not included due to their confounding impact on motor function and the lack of consensus over antidepressant effects.

To be included in the meta-analysis, a study had to include patients with idiopathic PD only, be a depression treatment study and enroll subjects diagnosed with depression, use a medication approved as an antidepressant in the United States or Europe, and report the change over the course of treatment based on a standardized rating scale of depression severity. Although more restrictive criteria were considered, using them would have eliminated almost all studies from inclusion, and the authors decided that less restrictive criteria would have would have made the sample too heterogeneous in terms of neurological diagnosis, medication utilized for the treatment of depression, and the measurement of treatment outcome.

There were two reviewers for the articles (D.W. and P.J.M.). The reviewers met monthly during the literature review, statistical analysis, and article preparation, and there was agreement between the reviewers on the findings of the reviewed articles.

Statistical Analysis

Analyses were conducted according to procedures suggested by Rosenthal[20] and Hedges and Olkin.[21] *Comprehensive Meta-Analysis v. 1.10* software (Biostat, Englewood, NJ) was used to calculate effect sizes and to carry out subsequent homogeneity and moderator variable analysis. The dependent measure was effect size for baseline and posttreatment ratings of depression expressed in Cohen's *d*.[22,23] Traditionally, Cohen's *d* index is the difference between patient and control group means, within each study or comparison, expressed in standard deviation units. Here, *d* is expressed as the change from baseline for each study. If the means and standard deviations were not reported, approximate *P* values were converted to *d* using formulas provided by Glass.[22] By expressing effect size in standard deviation units, we were able to make a direct comparison of outcomes across studies. The analysis proceeded in two steps. First, Cohen's *d* was derived for each study by subtracting the mean baseline depression score (m_b) from the mean follow-up depression score (m_p), and dividing it by the pooled standard deviation (s) using the formula of Rosnow and Rosenthal[24]:

$$d = \frac{m_b - m_p}{s\sqrt{\frac{df}{N}}} \quad (1)$$

where $s = [(n_b - 1)s_b^2 + (n_p - 1)s_p^2]/(n_b + n_p - 2)$ df = degrees of freedom and N = the total number of observations. An effect size ≥0.80 was considered large, as described by Cohen's metric.[25]

Individual values of *d* were hereafter combined across studies and weighted according to their variance estimate (v) using the formulas:

$$d_s = \frac{\sum w_i d_i}{\sum w_i}, \quad (2)$$

where $w_i = \frac{1}{v_i}$ represents the individual weight for a given study and vi is the variance of d_i.[21]

Potential differences in effect size between treatment and placebo administration were analyzed using the method of Hedges and Olkin.[21] This procedure computes mean weighted effect sizes and 95% confidence intervals (CI) for each level of a variable (i.e., treatment condition), and

allows for the testing of the influence of each individual factor on the overall results. The 95% CI is calculated as

$$d_s \pm 1.96\sqrt{v_s},$$

where $v_s = \frac{1}{\sum w_i}$.

Moderator Variable Analysis

Age, gender, and severity of PD (i.e., Hoehn and Yahr stage) have been cited as possible contributors or moderator variables in the expression of depression in PD. These variables, plus sample composition (major depression only vs. mixed depression) and duration of trial, were therefore examined as potential moderators of the obtained effect sizes. Continuous data (i.e., mean age of sample, percentage of sample that was male, mean Hoehn and Yahr stage, and mean duration of clinical trial) were analyzed with a meta-regression model, which is equivalent to a weighted least-squares regression model with weights equal to w_i.[26] For each continuous moderator variable of interest, the following model was estimated:

$$\theta_i = \beta_0 + \beta_1 x_i,$$

where θ_i represents the effect size estimate for each study and xi is the moderator variable of interest. A nonsignificant test of H_0: $\beta_1 = 0$ suggests there is insufficient evidence of a relationship between the predictor variable and effect size. Meta-regression models were fit in *SPLUS v6* (Insightful Corp., Seattle, WA).

Group comparisons were made for categorical moderator variables (e.g., sample composition). In these comparisons, an analysis of variance (ANOVA)-type summary is estimated for the group effect.[27]

Significance tests for these analyses were two-tailed. Given the small number of study groups in the meta-analysis that were administered placebo, only the active treatment groups were subjected to moderator variable analysis. *P* values ≤0.05 were considered significant.

To gauge the relative magnitude of the observed treatment effects for depression in patients with PD, effect sizes were also calculated for the two largest placebo-controlled antidepressant studies in elderly outpatients with major depression but without PD.[28,29]

RESULTS

Review of Studies

Publication Date—Between 1 January 1965 and 31 December 2003, a total of 27 studies were identified[5,14,30-54] that met inclusion criteria. Although the examined timeframe was 37 years, half (14/27, 51.9%) of the studies had been published in the past seven years.[5,14,32,34,36-38,41,47,48,50-52,54]

Study Design—Approximately half (16/27, 59.3%) of the studies were designed as antidepressant studies; the rest were designed primarily to measure the change in PD symptoms and did not specifically include patients with a depression diagnosis, although they did include change in depression as a secondary outcome measure.[30,33,34,39,40,42,43,45,46,49,53] Eleven of the studies were double-blind placebo-controlled,[5,14,30,31,35,42,43,45,46,49,53] one combined subjects from a double-blind placebo-controlled and an open-label study,[40] one was a double-blind comparison study,[39] two were single-blind placebo-controlled,[33,34] and twelve were open-label studies.[32,36-38,41,44,47,48,50-52,54]

Twenty-four of the studies specified trial duration, and their mean (range) duration was 12.6 (range, 1-65) weeks. Another study treated patients for between 2 and 5 months,[34] and one other did not provide any information about duration of treatment.[46]

Sample Size—In total, 772 subjects enrolled in the studies, and there were 668 completers (overall completion rate = 86.5%). Mean study sample size was 28.6 (range, 8-93).

Inclusion Criteria—Thirteen (48.1%) of the studies used formal diagnostic criteria to define depression (12 Diagnostic and Statistical Manual for Mental Disorders [DSM-IV or DSM-IIIR] criteria[5,14,35-38,41,47,50-52,54] and 1 Feighner's criteria[44,55]). For the studies using DSM criteria, six included patients with major depression only,[5,14,38,47,51,52] four enrolled patients with major depression or dysthymia,[36,37,41,50] and two included patients with a depression diagnosis but did not specify further.[35,54] Three studies using formal diagnostic criteria also used a minimum score on a depression rating scale as an additional inclusion criterion.[44,47,54] Three other studies used only a minimum score on a depression rating scale as an inclusion criteria and did not formally diagnose depression.[31,32,48] The other 11 studies were not designed as depression studies and either did not attempt to diagnose depression at baseline or did not specify such attempts.[30,33,34,39,40,42,43,45,46,49,53]

For the six studies that required a minimum score on a scale of depression severity as an inclusion criterion, three required a minimum score on the Hamilton Depression Rating Scale[56] (two >16, one >17),[44,47,54] one a Montgomery Asberg Depression Rating Scale[57] score >7,[32] one a Geriatric Depression Scale-Short Form[58] score >4,[48] and one an Andersen Depression Scale[59] score >12.[31]

Study Medication—Approximately half (15/27, 55.6%) of the studies used FDA-approved medications for the treatment of major depression. Ten studies utilized selective serotonin reuptake inhibitors (SSRIs); four used citalopram,[5,32,50,51] three sertraline,[14,41,48] two paroxetine,[36,54] and one used four different SSRIs.[37] Four studies used tricyclic antidepressants (one each imipramine,[53] desipramine,[45] amitriptyline,[43] and nortriptyline[31]), and bupropion was utilized in one study.[40]

Examining dosages for the antidepressants most commonly used in these studies (i.e., SSRIs), all studies included dosages within the therapeutic range for geriatric depression as recommended by experts but only one[32] included a dosage within the highest recommended range.[60]

Examining non-FDA-approved medications, three studies used antidepressants prescribed outside of the United States (one each moclobemide,[52] reboxetine,[47] and nomifensine[34]). PD medications were assessed for antidepressant effects in seven studies (six used selegiline[30,33,39,42,46,49] and one, bromocriptine[44]). Finally, *S*-adenosyl-L-methionine (SAMe), an amino-acid derivative that has been studied for its antidepressant effects, was used in two studies.[35,38]

Outcome Measures—Most studies (22/27, 81.5%) used a depression severity rating scale as the primary outcome measure. Thirteen studies used the Hamilton Depression Rating Scale,[5,30,35-38,42,44,47,50-52,54] four the Zung Scale,[39,43,46,49] two the Montgomery Asberg Rating Scale,[14,32] and one each the Anderson Scale,[31] the Beck Depression Inventory,[41,62] and the Profile of Mood States.[33,63] The other five studies did not use a formal outcome measure.[34,40,45,48,53]

Only 2 of 22 studies using a depression severity rating scale defined response a priori either as a minimum percentage of improvement in the scale or a study completion scale score below

a specified number.[14,51] The 5 studies that did not use a formal outcome measure defined response as being "improved,"[40,45,48] "cured,"[34] or as the "degree of relief."[53]

Statistical Analysis—Statistical tests used were Mann-Whitney *U* or Wilcoxon signed-rank tests,[5,31,32,38,41,43,47,49] analysis of variance for repeated measures,[30,33,35-37,39,50] *t* test,[42,44,52] and χ^2 test.[14]

Six studies reported "percentage improved,"[34,40,45,48,51,53] and two others did not specify the statistical technique used.[46,54] Only two of these studies were designed as antidepressant studies[48,51] and only one reported a *P* value for depression outcome.[54]

Results—Fourteen (14/20, 70.0%) of the studies using statistical tests reported $P < 0.05$ in favor of treatment,[30,33,35-37,41,50] including seven with $P < 0.01$.[31,32,38,44,47,52,54] The other six studies reported nonsignificant *P* values.[5,14,39,42,43,49] For the six studies reporting "percentage improvement," four studies reported that a total of 59.0% (36/61) of subjects improved with treatment,[40,48,51,53] one reported "no improvement" with treatment,[34] and the other reported the percentage improvement only for a subset of the sample.[45]

Examining double-blind, placebo-controlled studies (n = 11), six reported no statistically significant difference between active and placebo treatment,[5,14,42,43,46,49] three reported $P < 0.05$,[30,31,35] one stated that 60.0% (12/20) of subjects "improved" on active treatment but did not specify improvement on placebo,[53] and one study did not report results.[45]

Meta-Analysis

Of 27 antidepressant studies originally identified, 11[5,14,32,36,37,41,47,50-52,54] met criteria for inclusion in the meta-analysis. Two[5,14] of the studies included in the meta-analysis were placebo-controlled, and the active and placebo treatment arms for these studies were analyzed separately. Altogether, 309 subjects were enrolled, 260 in open-label and 49 in placebo-controlled studies. The characteristics and effect sizes for each of the 13 study treatment groups (11 active treatment and 2 placebo) are presented in Table 1.

Excluded studies were those that utilized as antidepressants medications that are prescribed primarily to treat the motor symptoms of PD (n = 7[30,33,39,42,44,46,49]) or are not approved for the use of depression in the United States or Europe (n = 2[35,38]), presented incomplete or unusable data (n = 6[31,34,40,45,48,53]) or used grossly inadequate antidepressant dosages (n = 1[43]).

Group Treatment Effects

Analysis of both active treatment and placebo condition revealed a very large composite effect size ($d_+ = +0.95$; 95% CI = $+0.76 < \delta < +1.14$), reflecting significant reductions in depression ratings after both antidepressant treatment and placebo administration. Between-treatment analysis, however, indicated that the effect size for active treatment was not significantly different from that for placebo ($Q_B = 0.59$, $P = 0.44$; Table 2).

Homogeneity analysis, testing the equality of effect sizes across studies, revealed significant heterogeneity of effect sizes in the active treatment studies ($Q[10] = 29.80$, $P < 0.001$). The hypothesis of homogeneity was rejected at the 5% level, indicating differences between the study effect sizes. Removal of three outliers[36,37,41] yielded a more homogeneous sample ($Q[7] = 10.2$, $P = 0.18$) with the mean effect size for active treatment studies increasing by 44% with removal of these outliers ($d_+ = +1.34$, 95% CI = $+1.07 < \delta < +1.61$).

The composite effect size for the placebo treatment groups was homogeneous ($Q[1] = 0.47$, $P = 0.49$). Repeat contrasts between active treatment and placebo groups for the homogeneous

solutions remained not significant ($Q_B = 0.43$, $P = 0.51$), indicating that both conditions produced very large, but similar, reductions in depression severity.

Moderator Variable Analysis

Age—The mean age across studies (N = 11 studies) was 66.1 years. The impact of age on the obtained effect sizes for active treatment was significant ($t = 1.92$, $P = 0.05$), with older age being associated with a larger effect size.

Gender—The composition of samples with regard to men and women was assessed by calculating the percentage of men in each sample and relating this to effect size. The percentage of men in the studies (N = 9 studies) combined was 54%, suggesting an equitable balance between men and women in the studies analyzed. Examination of gender effects on treatment response did not reveal any significant impact of this factor on effect size ($Z = 1.16$, $P = 0.25$).

Severity of PD—The average Hoehn and Yahr score was 2.3. Severity of PD did not have a significant impact on the obtained effect sizes (N = 8 studies; $t = 1.62$, $P = 0.11$).

Diagnostic Composition of Sample—To examine the possible impact of diagnostic composition of the samples (N = 11 studies) on effect size, each study sample was classified as consisting of patients with: (1) major depression only, or (2) mixed depression (any combination of major depression, minor depression, dysthymia, and no criteria specified). Five studies were comprised of patients with major depression only, and six had a mixed depression sample. Analysis of effect size by diagnostic composition revealed significant differences between major depression and mixed depression ($Q_B = 12.2$, $P < 0.001$), with the studies comprised of a mixed depression sample having much smaller effect sizes ($d_+ = +0.84$, 95% CI = $+0.63 < \delta < +1.06$) than did those consisting of patients with major depression only ($d_+ = +1.49$, 95% CI = $+1.19 < \delta < +1.79$).

Duration of Trial—The mean trial duration across studies (N = 11 studies) was 11.9 weeks. The impact of duration on the obtained effect sizes for active treatment was significant ($t = -3.81$, $P < 0.001$), with longer studies associated with a smaller effect size.

Comparison with Treatment Effects in Non-PD Geriatric Depression Studies

The effect sizes for both active treatment ($d_+ = +1.42$, 95% CI = $+1.31 < \delta < +1.53$) and placebo ($d_+ = +1.24$, 95% CI = $+1.13 < \delta < +1.34$) conditions in non-PD elderly patients with major depression were larger than were those found in PD. In addition, active treatment was significantly superior to placebo condition in the non-PD population ($Q_B = 5.73$, $P = 0.02$).

DISCUSSION

Our literature review identified fewer than 30 studies over the past 40 years involving use of a medication with reported antidepressant effects for the treatment of depression in PD. Most published studies were conducted in the past decade, which coincided with the introduction of SSRIs and other newer antidepressants.

Concerning study design, only one-half were designed as antidepressant studies, and one-third used a medication not approved for the treatment of depression in the United States or Europe. Fewer than half the studies were placebo-controlled, and the average sample size was less than 30 subjects. Less than half the studies used formal diagnostic criteria to diagnose depression, and less than one-fifth used a depression rating scale to set a minimum depression severity for study inclusion. Although most studies used a rating scale of depression severity to assess outcome, almost none defined a priori what constituted response to treatment.

Of 27 studies originally identified, only 11 were determined to be suitable for inclusion in the meta-analysis. The most common reasons for excluding studies were study designs testing the impact of an antidepressant on parkinsonism instead of depression, the use of PD or unapproved medications as antidepressants, and inadequate or insufficient data to compute a treatment-effect size.

The results of the meta-analysis results suggest a very large effect for both active treatment and placebo in PD depression, but no difference between the two. Creating homogenous samples by removing the three outlying studies from the active treatment analysis increased the effect size for active treatment substantially, but there still was no difference between the two conditions. Nonspecific treatment elements, not medication effect, thus may be the reason for the positive response reported in PD antidepressant studies. The number of placebo-controlled studies, however, was very small.

In contrast, the largest placebo-controlled antidepressant studies in elderly patients without PD found active treatment to be superior to placebo. As both PD and non-PD depressed patients showed a similar robust response to placebo condition, the difference seemed to be that PD patients did not respond as well to active treatment as did non-PD patients. This was despite the fact that the overwhelming majority of PD patients included in the meta-analysis who were treated with an antidepressant were in open-label studies, whereas the non-PD patients taking an antidepressant were enrolled in placebo-controlled studies, which typically report lower response rates. Removal of the three outlying studies did make the effect sizes for active treatment comparable in the two groups, suggesting that variability in study design (e.g., use of mixed depression samples) may help explain the lower response rates to active treatment in PD.

Examining moderators of treatment response, age and diagnostic composition were two of the variables associated with treatment response. Specifically, increasing age was associated with a better response to treatment, showing that old age should not be considered a barrier to treatment for depression in PD.

Studies that enrolled patients with a variety of depression diagnoses (i.e., mixed depression samples) showed less treatment effect than did those that restricted enrollment to patients with major depression. This is not surprising, as it is thought that patients with minor depression or dysthymia are less likely to respond to antidepressant treatment than are patients with more severe depression.[64,65] All three outlier studies had mixed depression samples, suggesting that part of the failure to demonstrate a difference between active treatment and placebo conditions in PD was due to the inclusion of patients with less severe forms of depression in some studies.

Concerns linger about the ability of PD patients to tolerate newer antidepressants, particularly in terms of worsening parkinsonism.[66] Although the data on tolerability did not lend itself to statistical analysis, it is important to note that for the studies included in the meta-analysis, 87.3% (227/260) of subjects completed open-label trials, including 86.3% (202/234) of those taking an SSRI. In addition, 79.2% (19/24) of subjects in placebo-controlled trials completed active treatment. These findings suggest that PD patients in general are able to tolerate SSRI treatment.

The meta-analysis was limited by the overall lack of consistency in following guidelines for the statistical reporting of clinical trials,[67] particularly for older studies. Second, the analysis used effect size formulas for independent samples, but the effect size estimates were based on change in depression score from baseline, which are not independent measures. Third, pooling the estimates of the variances from the two time points yields an overestimate of the true variance of the difference. Fourth, there were two studies with sample sizes less than 10;

however, there was very little difference in the effect size estimate for the active treatment after removing the small studies ($d_+ = +0.89$, 95% CI = $+0.69 < \delta < +1.10$). Fifth, a limitation of all meta-analyses is that only published studies are included, so the possibility of publication bias suggests that active treatment effect sizes may actually be less than reported here. Finally, almost all studies included in the meta-analysis used SSRIs, limiting the conclusions that can be drawn about antidepressant treatment in general.

In conclusion, although depression and antidepressant use is common in PD, there have been surprisingly few antidepressant studies and almost no controlled research in this population. Meta-analysis results suggest that antidepressant treatment has a very large but nonspecific positive effect on depression in PD. In addition, PD patients may benefit less from antidepressant treatment than elderly depressed patients without PD do, although this may be due partly to diagnostic heterogeneity in study populations.

The paucity of existing data highlights the need to conduct large-scale, placebo-controlled antidepressant studies in PD, to compare multiple classes of medications due to the unique pathophysiological changes in this disease, and to establish moderators and mediators of treatment response. To accomplish the latter, studies should include subjects with a wide range of ages, cognitive abilities, depression severity, and PD clinical characteristics.

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TABLE 1

Summary of antidepressant studies included in meta-analysis

Reference	Rating scale	Pre/ posttreatment mean (SD) or [SE]	Medication	Depression diagnosis	n	Gender (%) male	Mean age (yr)	Mean PD stage	Trial length (wk)	Effect size (Cohen's *d*)
Aarsland et al., 2000[32]	Melancholia	19.2 (9.2)/ 6.1 (5.2)	Citalopram	Mixed	11	67	72.7	—	8	1.75
Ceravolo et al., 2000[36]	BDI, HDRS	—	Paroxetine	Mixed	29	55	63.3	2.1	26	0.53[a]
Dell' Agnello et al., 2001[37]	BDI, HDRS	—	Citalopram	Mixed	52	55	62.9	2.2	26	0.39[a]
			Fluoxetine Fluvoxamine Sertraline							
Hauser and Zesiewicz, 1997[41]	BDI	16.0 [2.0]/ 11.7 [1.9]	Sertraline	Mixed	13	—	69.6	—	7	0.59
Leentjens et al., 2003[14]	MADRS	Tx 19.8(5.1)/ 11.3(10.4)	Sertraline	Major	Tx6	Tx 67	Tx 64.8	2.2	10	Tx 1.04[a]
		PI 18.8(6.6)/ 8.0 (4.0)			PI 6	PI 67	PI 68.5			PI 1.99[b]
Lemke, 2002[47]	HDRS (17-item)	18.6 (3.0)/ 12.2 (3.3)	Reboxetine	Major	15	47	66.9	2.4	4	2.04
Rampello et al., 2002[50]	BDI, HDRS	—	Citalopram	Mixed	16	—	64.0	2.8	17	0.73[a]
Rihmer et al., 2000[51]	HDRS (17-item)	20.4 (1.2)/ 9.1 (5.2)	Citalopram	Major	8	75	74.1	2.4	8	2.99
Steur and Ballering, 1999[52]	HDRS (17-item)	23.2 (7.6)/ 12 (5.1)	Moclobemide	Major	10	40	58.2	3.1	6	1.73
Tesei et al., 2000[54]	HDRS	21.7 (6.4)/ 13.8 (5.8)	Paroxetine	Mixed	52	40	66.6	2.6	13	1.29
Wermuth et al., 1998[5]	HDRS (17-item)	Tx 16.6(3.5)/ 11.7(4.5)	Citalopram	Major	Tx 18	Tx 33	Tx 65.9	—	6	Tx 1.22
		PI 16.2(3.1)/ 11.7(4.9)			PI 19	PI 53	PI 63.4			PI 1.10

SD, standard deviation; SE, standard error; PD, Parkinson's disease; BDI, Beck Depression Inventory; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; Tx, active treatment; Pl, placebo condition.

[a] Effect size computed from $P = 0.049$

[b] Mean and standard deviations obtained from author.

TABLE 2

Tests of categorical model for positive response by treatment assignment in PD patients with depression

Treatment	k	$d_{+0.93}$	95% CI	Q_w
Active treatment	11	+0.93	+0.73 < δ < +1.13	29.80[a]
Placebo	2	+1.18	+0.55 < δ < +1.81	0.47

Q_B (between-class effect) = 0.59, P = 0.44.

Treatment, active treatment vs. placebo administration; k, number of studies in analysis; d_4, mean weighted effect size; 95% CI, 95% confidence interval for d_+; Q_W, within-class effect (test for homogeneity).

[a] $P < 0.001$.