Efficacy of Antidepressants for Late-Life Depression: A Meta-Analysis and Meta-Regression of Placebo-Controlled Randomized Trials

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ABSTRACT

Objective: Late-life depression is an important public health issue, given the growing proportion of the elderly relative to the general population in the developed world. The purpose of this study was to examine the efficacy of antidepressants for the treatment of major depressive disorder (MDD) in elderly patients.

Data Sources: PubMed/MEDLINE was searched for randomized, double-blind, placebo-controlled trials of antidepressants for treatment of both adult (nonelderly) MDD (patients aged < 65 years) and late-life MDD (patients aged ≥ 55 years). The search was limited to articles published between January 1, 1980, and March 3, 2010 (inclusive). The year 1980 was used as a cutoff in our search to decrease diagnostic variability, since the *DSM-III* was introduced in 1980. Our search cross-referenced the term *placebo* with each of the following antidepressants: *amitriptyline*, *nortriptyline*, *imipramine*, *desipramine*, *clomipramine*, *trimipramine*, *protriptyline*, *dothiepin*, *doxepin*, *lofepramine*, *amoxapine*, *maprotiline*, *amineptine*, *nomifensine*, *bupropion*, *phenelzine*, *tranylcypromine*, *isocarboxazid*, *moclobemide*, *brofaromine*, *fluoxetine*, *sertraline*, *paroxetine*, *citalopram*, *escitalopram*, *fluvoxamine*, *zimelidine*, *tianeptine*, *trazodone*, *nefazodone*, *agomelatine*, *venlafaxine*, *desvenlafaxine*, *duloxetine*, *milnacipran*, *reboxetine*, *mirtazapine*, and *mianserin*. We also reviewed the reference lists of all studies identified through the PubMed/MEDLINE search.

Study Selection: Articles were selected that reported on randomized, double-blind, placebo-controlled trials of antidepressants used as monotherapy for treatment of MDD and that met numerous a priori criteria pertaining to MDD diagnosis criteria, study duration, study design, drug formulation, original data, age thresholds, primary and secondary outcome measures, and exclusions of other disorders. Final inclusion of articles was determined by consensus between the authors. Seventy-four articles were found eligible for inclusion in our analysis (15 late-life MDD trials and 59 adult MDD trials).

Results: Antidepressants were found to be efficacious for late-life MDD (age 55 and older; $P < .0001$), although there was evidence for heterogeneity across studies ($Q_{22} = 67.302$, $P < .001$). However, antidepressants were not found to be efficacious in the subset of studies using age thresholds of 65 years or older (*older* late-life MDD) ($P = .265$). Finally, when we controlled for study design characteristics, antidepressant but not placebo response rates were lower among late-life MDD patients than among adult MDD patients.

Conclusions: The present meta-analysis suggests that antidepressants are efficacious in late-life MDD, but significant study heterogeneity suggests that other factors may contribute to these findings. A secondary analysis raises the possibility that efficacy of these agents may be reduced in trials involving patients aged 65 years or older. Why antidepressants may be less efficacious in elderly versus younger subjects remains unclear.

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Major depressive disorder (MDD) is a highly prevalent illness. The World Health Organization estimates the 12-month prevalence of MDD in developed countries to be between 3.1% (in Japan) and 9.6% (in the United States).[1] Due to increased rates of morbidity, mortality, and functional impairment, MDD has repeatedly been shown to contribute to a significant financial and societal burden in developed and developing nations.[2] Among older adults, MDD (termed *late-life MDD*) is the most prevalent psychiatric disorder, estimated to be present in 9%–18% of the population over 55 years of age.[3–5] Older depressed subjects are at increased risk for comorbid chronic illness and functional impairment. Their mortality risk has been estimated to be 2- to 3-fold higher than for nondepressed elderly individuals, with suicide as well as complications of cardiac disease accounting for a significant proportion of the increase in risk.[6,7] Unfortunately, however, late-life MDD is often underrecognized and undertreated, with patients often receiving subtherapeutic doses of antidepressants.[8]

Most of our knowledge regarding the efficacy of antidepressants for the treatment of MDD derives from randomized, double-blind, placebo-controlled trials that typically exclude patients over 65 years of age.[9–15] As a result, the majority of patients enrolled in placebo-controlled antidepressant treatment trials are young adults (mean age = 40 years) with few comorbid Axis I or Axis III disorders. Therefore, separate clinical trials are required in order to establish whether antidepressant agents are effective and safe in older patient populations who typically also present with a greater burden of comorbid Axis III disorders. Fortunately, a number of randomized, double-blind, placebo-controlled trials have thus far been conducted evaluating the efficacy, safety, and tolerability of antidepressants as monotherapy for late-life MDD. A recent meta-analysis[16] pooling 10 of these trials had concluded that antidepressants were more efficacious than placebo for late-life MDD, although a mere 9.7% advantage in response rates between the 2 treatment groups was noted. In addition, while placebo response rates reported for late-life MDD in that analysis (34.7%) were comparable to placebo response rates in an analysis of adult MDD studies (37.3%),[17] response rates for antidepressant-treated patients appeared to be much lower in late-life MDD trials than in adult MDD trials (44.4% vs 53.8%, respectively). One limitation, however, of this meta-analysis[16] was that it focused only on the use of second-generation antidepressants. Therefore, the purpose of the present meta-analysis was to examine the efficacy of all antidepressants, whether older or newer, in late-life MDD and to compare both antidepressant and

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Clinical Points

- Late-life major depressive disorder (MDD) is often underrecognized and undertreated even though it is the most prevalent psychiatric disorder, estimated to be present in 9%–18% of the population over 55 years of age.
- Antidepressants are efficacious in the treatment of late-life MDD, but antidepressant response rates are lower than in adult MDD (< 65 years).
- Executive dysfunction, comorbid Axis III conditions, greater chronicity of depressive episode, and undertreatment might influence antidepressant response specifically in patients older than 65 years.

placebo response rates from clinical trials examining patients with adult MDD and late-life MDD.

METHOD

Data Sources and Search Strategy

We sought to identify double-blind, randomized, placebo-controlled trials of antidepressants used as monotherapy for the treatment of patients with adult MDD and late-life MDD for possible inclusion in the meta-analysis. Adult MDD trials included patients aged < 65 years. An age threshold of 55 years was used for the late-life MDD group because this age was used as a threshold in several older trials as well as in other meta-analyses[18] and, therefore, to avoid the exclusion of data that would have resulted had we chosen 65 years of age (used by most regulatory authorities world-wide) as the cutoff. For antidepressants, we defined pharmacologic agents as those that had received a letter of approval by the US, Canadian, European Union, Japanese, or Australian drug regulatory agencies for the treatment of MDD. According to this definition, the following pharmacologic agents met criteria to be considered as antidepressants: *amitriptyline*, *nortriptyline*, *imipramine*, *desipramine*, *clomipramine*, *trimipramine*, *protriptyline*, *dothiepin*, *doxepin*, *lofepramine*, *amoxapine*, *maprotiline*, *amineptine*, *nomifensine*, *bupropion*, *phenelzine*, *tranylcypromine*, *isocarboxazid*, *moclobemide*, *brofaromine*, *fluoxetine*, *sertraline*, *paroxetine*, *citalopram*, *escitalopram*, *fluvoxamine*, *zimelidine*, *tianeptine*, *trazodone*, *nefazodone*, *agomelatine*, *venlafaxine*, *desvenlafaxine*, *duloxetine*, *milnacipran*, *reboxetine*, *mirtazapine*, and *mianserin*.

Eligible studies were identified by PubMed/MEDLINE searches that cross-referenced the term *placebo* with each of the above-mentioned agents. The PubMed/MEDLINE search was limited to articles published between January 1, 1980, and March 3, 2010 (inclusive). The year 1980 was used as a cutoff in our search to decrease diagnostic variability, since the *DSM-III* was introduced in 1980. To expand our database, we then reviewed the reference lists of all studies identified through the PubMed/MEDLINE search. Final inclusion of articles was determined by consensus between the authors.

Study Selection

We selected randomized, double-blind, placebo-controlled trials of antidepressants used as monotherapy for the treatment of MDD that met all of the following criteria:

1. Defined MDD according to the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition[19]; *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised[20]; *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition[21]; Research Diagnostic Criteria[22]; or the Feighner diagnostic criteria.[23]
2. Were 4 weeks in duration, or longer.
3. Involved the use of a parallel (not crossover) design.
4. Employed oral formulations of antidepressants.
5. Presented entirely original (not previously published) data.
6. Enrolled either adult MDD patients aged < 65 years or late-life MDD patients aged ≥ 55 years.
7. Excluded treatment of patients with treatment-resistant depression or patients with other depressive disorders, including bipolar disorder, depression with psychotic features, dysthymic disorder, neurotic depression, or minor depression.
8. Excluded treatment of MDD in patients with comorbid alcohol disorders, substance use disorders, or a specific comorbid medical illness (eg, Alzheimer's dementia, Parkinson's disease).
9. Employed the Hamilton Depression Rating Scale (HDRS),[24] the Montgomery-Asberg Depression Rating Scale (MADRS),[25] or the Clinical Global Impressions-Improvement scale (CGI-I)[26] as one of their outcome measures.

Definitions

Clinical response was defined as a 50% or greater reduction in HDRS or MADRS scores, from baseline to endpoint, or a CGI-I score < 3 at the final visit. For consistency, the HDRS was chosen over the MADRS or CGI-I when response rates from multiple scales were reported. For studies that reported only CGI-based response rates, HDRS-based response rates were either obtained from the sponsor or imputed using the method of Walsh et al.[27] Discontinuation rates were defined as per each protocol. For consistency, we used intent-to-treat–based response rates in the present analysis. Whenever intent-to-treat–based response rates were not available in the publication, the sponsor was contacted to obtain intent-to-treat–based response rates. In cases in which the sponsor could not retrieve intent-to-treat–based response rates, we utilized response rates based on completers. The probability of receiving placebo was computed from the number of treatment arms and the randomization schedule (ie, 1:1:1) of each trial. For example, a 2-arm trial with a 2:1 randomization favoring antidepressant treatment yields a 1 in 3 chance of receiving placebo.

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Quantitative Data Synthesis

In the present meta-analysis, we included and compared trials in adult MDD and late-life MDD ("comprehensive analysis"). Age 55 years was chosen as the threshold for defining late-life MDD in order to present more comprehensive analyses, since several older antidepressant trials had chosen this age rather than 65 as a cutoff. However, in recognition that there is overlap in the age ranges (between 55 and 65 years), we also conducted a secondary "nonoverlap" analysis by comparing studies of adult MDD with studies of *older* late-life MDD that used thresholds of 65 years or older.

The study analyses were conducted as follows:

- First, random-effects meta-analyses were utilized to estimate the pooled risk ratio (RR) of responding to antidepressants versus placebo in late-life MDD trials and in adult MDD trials.
- Second, a meta-regression was used to compare the RR of responding to antidepressants versus placebo between the 2 clinical trial groups (adult MDD vs late-life MDD). For this meta-regression, the year of publication, severity at baseline, study duration, and probability of being randomized to placebo were also entered as covariates since they had also previously been found to influence the RR of clinical response to antidepressant versus placebo therapy.[16,17]
- Third, a meta-regression was conducted to compare the RR of discontinuing antidepressants versus placebo between these 2 clinical trial groups (adult MDD vs late-life MDD). For this meta-regression, only study duration was entered as a covariate since no other variable had previously been found to influence the RR of discontinuing antidepressants versus placebo.[28]
- Fourth, the analyses mentioned above were repeated comparing adult MDD versus older late-life MDD (nonoverlap analysis).
- Fifth, antidepressant response rates between study groups (adult MDD vs late-life MDD and adult MDD vs older late-life MDD) were compared using analysis of variance. In addition to sample size, the probability of being randomized to placebo, type of dosing (fixed vs flexible), and study duration were also entered as covariates since they have previously been found to predict antidepressant response rates.[16,17]
- Sixth, placebo response rates between study groups (adult MDD vs late-life MDD and adult MDD vs older late-life MDD) were compared using analysis of variance. In addition to sample size, the severity at baseline, year of publication, study duration, and probability of being randomized to placebo were also entered as covariates since they have previously been found to predict placebo response rates.[16,17]

All tests conducted were 2-tailed, with α set at the .05 level.

RESULTS

Initially, 7,303 abstracts were identified in PubMed/MEDLINE. Of these, 6,878 were excluded (they were reports that addressed other topics, were reviews, or were not randomized controlled trials of antidepressants). Abstracts for the remaining 425 clinical trials of antidepressants in MDD were obtained and were reviewed thoroughly. Fifteen additional articles were identified after we reviewed the reference lists of these 425 articles as well as the reference lists of 2 large meta-analyses. Of the 440 potential trials, 366 were excluded for the reasons listed in Figure 1.

Thus, a total of 74 reports were found eligible for inclusion in our pooled analysis (list available upon request). Fifteen of these[29–43] were randomized controlled trials in late-life MDD (utilizing an age threshold of 55 years), and 59 were adult MDD trials (utilizing an upper age of < 65 years). For the adult MDD trials, 51 (86.4%) were focused on outpatients, 3 (5.1%) on inpatients, and 5 (8.5%) on mixed inpatient-outpatient populations. For the late-life MDD trials, 14 (93.3%) were focused on outpatients and 1 (6.7%) on mixed inpatient-outpatient populations. Each of these articles reported the results of a single trial. These 74 trials included 132 antidepressant-versus-placebo contrasts and 20,572 patients, of whom 13,125 were randomized to an antidepressant and 7,447 to placebo. The 15 late-life MDD trials included 23 contrasts of antidepressants and placebo and included 4,756 patients, of whom 2,752 were randomized to an antidepressant and 2,004 to placebo. Specific description of the late-life trials is reported in Table 1.

Mean ages ± SD were 44.5 ± 2.7 and 69.7 ± 4.1 in the adult MDD and late-life MDD trials, respectively. There was no statistically significant difference in mean ± SD study duration in weeks (6.9 ± 2.9 vs 8.1 ± 2.2, respectively; $P = .131$), baseline severity in terms of HDRS score per treatment arm (21.4 ± 4.8 vs 21.7 ± 2.0, respectively; $P = .730$), probability of receiving placebo (35.0% ± 9.6% vs 38.9% ± 8.1%, respectively; $P = .165$), proportion of women (60.8% ± 11.0% vs 60.3% ± 8.6%, respectively; $P = .786$), number of assessments/appointments during the trial (5.6 ± 1.6 vs 6.0 ± 1.3, respectively; $P = .375$), or frequency of assessments/appointments (defined as the number of follow-up visits during the trial divided by the duration of the trial in weeks) (0.9 ± 0.2 vs 0.8 ± 0.2, respectively; $P = .211$) between adult MDD and late-life MDD trials. A statistically significant difference was found in the mean ± SD year of publication (1995 ± 7.4 years vs 2000 ± 8.6 years, respectively; $P = .041$) and sample size per treatment arm (94.1 ± 55.1 vs 125.2 ± 99.5, respectively; $P = .009$) between adult MDD and late-life MDD trials.

Meta-Analysis and Meta-Regression Results (comprehensive analysis)

The result of the random-effects meta-analysis indicated that antidepressant therapy resulted in statistically significantly higher response rates than placebo in late-life MDD studies (RR = 1.304; 95% CI, 1.150–1.479; $P < .001$)

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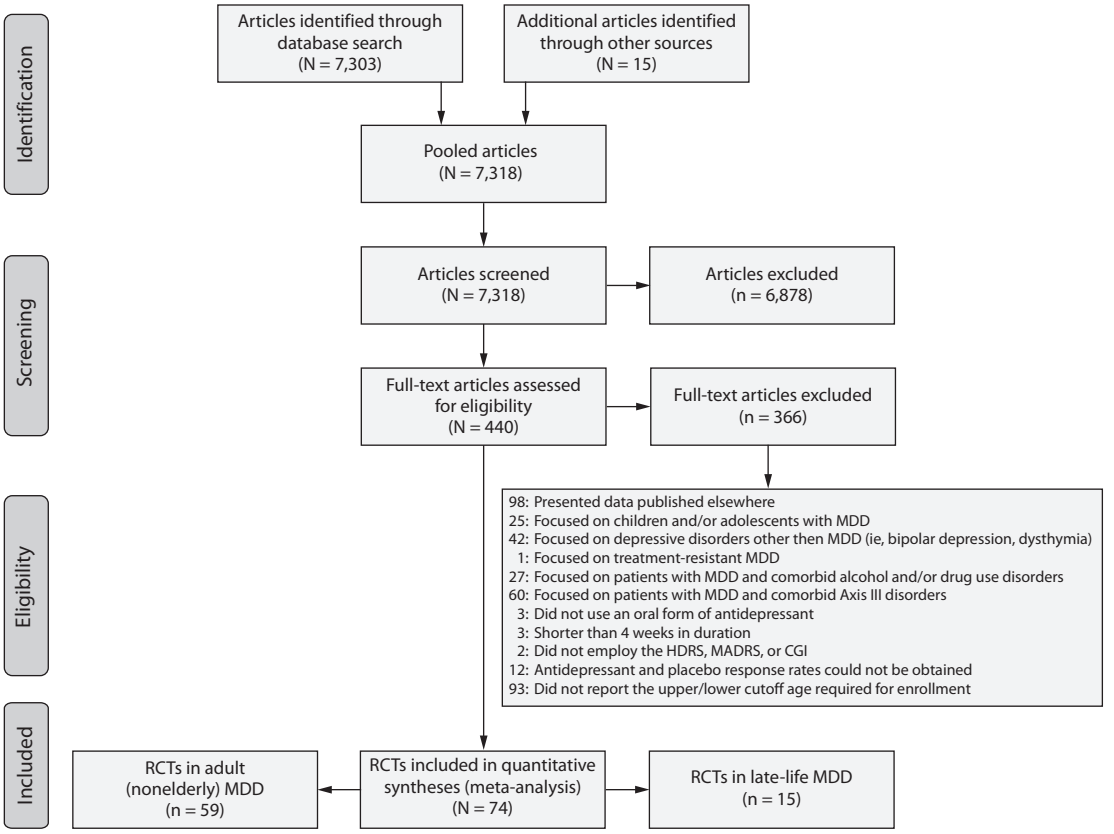
Figure 1. Flow Diagram of Trial Identification and Selection Process



Abbreviations: CGI = Clinical Global Impressions scale, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, RCT = randomized controlled trial.

(Figure 2). The RR for adult MDD studies was 1.420 (95% CI, 1.354–1.488; $P < .0001$). There was evidence for statistically significant heterogeneity (analyzed using Q statistic) in the RR for response to antidepressants versus placebo in the late-life MDD trials ($Q_{22} = 67.302$, $P < .001$) and in the adult MDD trials ($Q_{108} = 133.824$, $P = .047$).

Meta-regression analysis suggested no statistically significant difference in the RR of responding to antidepressant versus placebo (95% CI, −0.041 to 0.092; $P = .450$) and in the RR of discontinuing antidepressant versus placebo due to adverse events (95% CI, −0.087 to 0.294; $P = .288$) when comparing adult MDD and late-life MDD trials.

Meta-Analysis and Meta-Regression Results (nonoverlap analysis)

In the older late-life MDD studies that employed an age threshold of 65 or 75 years (mean patient age ± SD: 73.5 ± 3.0 years; 6 trials that included 8 contrasts of antidepressants vs placebo and involved 1,840 patients), the results of the random-effects meta-analysis indicated no statistically significant difference in response rates between antidepressant and placebo therapy (RR = 1.128; 95% CI, 0.929–1.369; $P = .265$). There was evidence for statistically significant heterogeneity in the RR for response to antidepressants versus placebo ($Q_7 = 22.925$, $P = .002$) in this group of trials.

Meta-regression analysis indicated that, in the adult MDD trials, the RR of responding to antidepressant versus placebo was statistically significantly higher (95% CI, 0.006–0.208; $P = .036$) than in the older late-life MDD studies, while, comparing these same 2 groups, no statistically significant difference was found in the RR of discontinuing antidepressant versus placebo due to adverse events (95% CI, −0.200 to 0.263; $P = .789$).

In light of the discrepancy of results (in terms of statistical significance of the main treatment effect) obtained when conducting the comprehensive analysis (ie, late-life MDD studies) and the nonoverlap analysis (ie, older late-life MDD studies), we conducted a post hoc meta-analysis specifically focusing on the late-life MDD trials that used an age threshold of 55 or 60 years. The 9 identified trials performed 15 contrasts and included 2,916 patients. Interestingly enough, we found that antidepressants were significantly more efficacious than placebo for this patient population (response rates for antidepressants and placebo of 46.5% [765/1,645] vs 29.8% [377/1,267], respectively; RR = 1.429; 95% CI, 1.241–1.645; $P < .0001$). There was evidence for statistically

Table 1. Trials of Antidepressants Versus Placebo in Late-Life Major Depressive Disorder (MDD)

Study (year)	Duration in Weeks	Treatment Arms, Dose per Day	Sample Size per Treatment Arm	Risk Ratio for Response	Lower Age Limit, y	Age, Mean (SD), y
Gerner et al (1980)[29]	4	1. Trazodone, 100–400 mg 2. Imipramine, 50–200 mg 3. Placebo	19 21 20	2.142 1.809	60	68.4[a]
Georgotas et al (1986)[30]	7	1. Nortriptyline, 25–125 mg 2. Phenelzine, 15–75 mg 3. Placebo	25 22 28	4.692 4.692	55	64.9 (6.1)
Halikas (1995)[31]	6	1. Mirtazapine, 5–35 mg 2. Trazodone, 40–280 mg 3. Placebo	49 48 49	1.457 1.171	55	62.0[a]
Nair et al (1995)[32]	7	1. Nortriptyline, 25–75 mg 2. Moclobemide, 100–400 mg 3. Placebo	38 36 35	1.105 0.921	60	69.7[a]
Tollefson et al (1995)[33]	6	1. Fluoxetine, 20 mg 2. Placebo	335 336	2.150	60	67.8 (5.7)
Schweizer et al (1998)[34,b]	8	1. Imipramine, 50–150 mg 2. Placebo	60 60	1.722	65	72.0 (6.7)
Rapaport et al (2003)[35]	12	1. Paroxetine CR, 12.5–50 mg 2. Paroxetine, 10–40 mg 3. Placebo	104 106 109	1.319 1.191	60	70.0 (6.0)
Schneider et al (2003)[36]	8	1. Sertraline, 50–100 mg 2. Placebo	371 376	1.346	60	69.8 (6.6)
Roose et al (2004)[37,b]	8	1. Citalopram, 10–40 mg 2. Placebo	84 90	1.081	75	79.6 (4.4)
Kasper et al (2005)[38,b]	8	1. Fluoxetine, 20 mg 2. Escitalopram, 10 mg 3. Placebo	164 173 180	0.787 0.978	65	75.0 (7.0)
Schatzberg and Roose (2006)[39,b]	8	1. Fluoxetine, 20–60 mg 2. Venlafaxine, 75–225 mg 3. Placebo	100 104 96	0.875 1.050	65	71.0 (5.0)
Raskin et al (2007)[40,b]	8	1. Duloxetine, 60 mg 2. Placebo	207 104	2.000	65	72.8 (5.6)
Bose et al (2008)[41]	12	1. Escitalopram, 10–20 mg 2. Placebo	130 134	1.210	60	68.3 (6.9)
Rapaport et al (2009)[42]	10	1. Paroxetine CR, 12.5 mg 2. Paroxetine CR, 25 mg 3. Placebo	168 177 180	1.300 1.450	60	67.0 (6.5)
Hewett et al (2009)[43,b]	10	1. Bupropion XR, 150–300 mg 2. Placebo	211 207	1.232	65	71.1 (5.8)

[a]No standard deviation was reported.
[b]Trials included in the nonoverlap analysis (older late-life MDD).
Abbreviations: CR = controlled release, XR = extended release.

significant heterogeneity in the RR for response to antidepressants versus placebo ($Q_{14} = 29.768$, $P = .034$) in this group of trials. These findings are different, in terms of treatment effect, than those obtained in the nonoverlap analysis (studies of older late-life MDD).

Results From Analysis of Variance

Antidepressant response rates were significantly lower for studies focusing on late-life MDD than for those focusing on adult MDD ($F = 8.43$, $P = .004$). Similarly, antidepressant response rates were significantly lower for studies focusing on older late-life MDD than for those focusing on adult MDD ($F = 7.34$, $P = .008$). (The number needed to treat was approximately 6 for adult MDD trials, 8 for late-life MDD trials, and 21 for older late-life MDD trials.) On the contrary, we found no statistically significant difference in placebo response rates when we compared studies focusing on adult MDD with studies focusing on late-life MDD ($F = 1.02$, $P = .320$) or older late-life MDD ($F = 0.00$, $P = .968$) (Figure 3).

DISCUSSION

In the present analysis, we examined the efficacy of all antidepressants, whether older or newer, for the treatment of late-life MDD. To do so, we pooled all clinical trials that focused on the treatment of elderly patients with MDD, with *elderly* being variably defined across studies as 55, 60, 65, or 75 years of age or older. Our results suggest that antidepressants are efficacious in the treatment of late-life MDD. However, statistically significant heterogeneity was detected. In fact, when we conducted a subanalysis focusing only on studies that employed an age threshold of 65 or 75 years to define older late-life MDD, we found no significant treatment effect for antidepressants versus placebo, while the significant heterogeneity in study results observed in the

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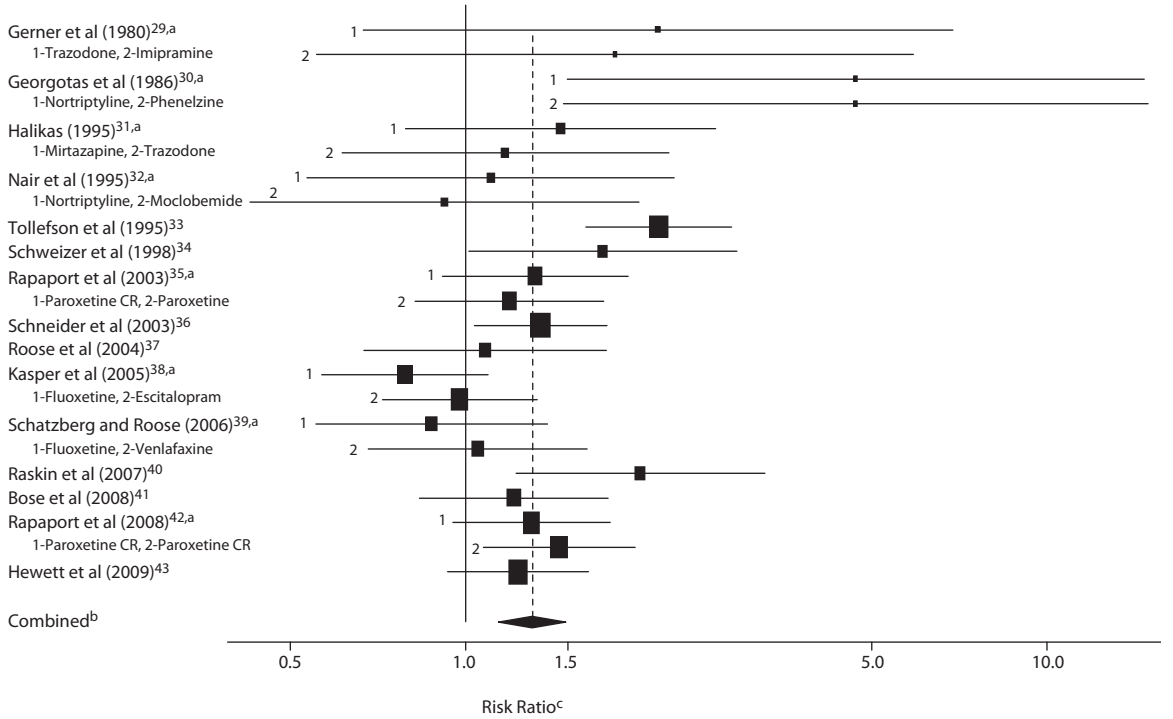
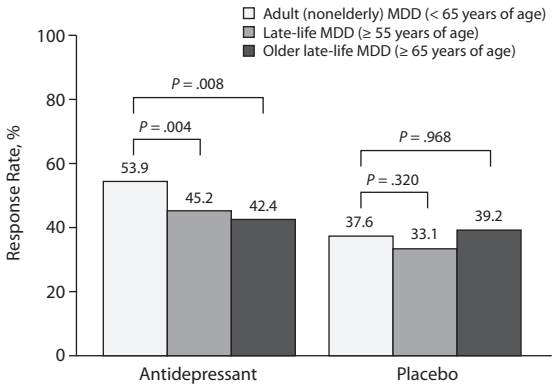
Figure 2. Effects of Antidepressants in Trials in Late-Life Major Depressive Disorder



[a]Studies reporting results of 2 antidepressant-placebo contrasts.
[b]Heterogeneity of combined studies: $Q_{22} = 67.302$, $P < .001$.
[c]The solid vertical line represents a risk ratio of 1; the dotted vertical line represents the pooled risk ratio; the boxes represent individual study risk ratios, with box size proportional to study sample size; the horizontal lines represent the 95% CI of the risk ratio (individual study or pooled).

Figure 3. Comparison (using analysis of variance) of Antidepressant and Placebo Response Rates in Younger Adult and Older Adult Patients[a]



[a]$P = .450$ for meta-regression comparing the risk ratio of antidepressant response versus placebo response in adult MDD studies versus late-life MDD studies; $P = .036$ for meta-regression comparing the risk ratio of antidepressant response versus placebo response in adult MDD studies versus older late-life MDD studies.
Abbreviation: MDD = major depressive disorder.

comprehensive dataset persisted. Interestingly enough, however, when we examined studies with an age threshold of 55 or 60 years, we observed a statistically significant treatment effect. In fact, the RR of 1.43 in late-life MDD trials using a threshold of 55 or 60 years was nearly identical to the RR of 1.42 for the adult MDD trials. Although preliminary, these findings raise the possibility that the reduced efficacy of antidepressants in late-life MDD may be accounted for by the older late-life MDD group. Discontinuation rates did not differ between adult MDD and late-life MDD studies.

Our study results, namely that antidepressants appear to be efficacious in late-life MDD but with significant heterogeneity in study findings across trials, are also in line with an earlier meta-analysis by Nelson et al[16] that focused on trials of second-generation antidepressants in late-life depression. In addition, similar to our meta-analysis, Nelson et al[16] reported that second-generation antidepressant response rates in this population (late-life MDD) appeared to be numerically lower than those reported for adult MDD patients. In the present analysis, we were able to confirm that, indeed, when we controlled for study design factors known to influence response rates, antidepressant but not placebo response rates reported in late-life MDD studies were significantly lower than those reported in studies of adult MDD patients.

Several factors could account for this finding. For example, executive dysfunction found in older patients with depression has been associated with a lower probability of antidepressant response (placebo response rates not considered).[44,45] Similarly, in a separate study,[46] delayed response inhibition on the digit-symbol performance test was associated with slower response to the selective serotonin reuptake inhibitor citalopram in elderly MDD patients. Other studies[47–49] have found that white-matter hyperintensities on

brain magnetic resonance imaging, which may be more common in older adults, predict poorer antidepressant response rates (placebo response rates not considered) in MDD patients. A greater burden of comorbid Axis III conditions[50] typically found in late-life MDD versus adult MDD populations may also explain our findings. Moreover, greater chronicity of a depressive episode has been associated with poor response to antidepressants, which, thus, could explain the lower response rates observed in late-life MDD patients.[51] Furthermore, the tendency to treat older patients with subtherapeutic doses of antidepressants might account for a lower response to antidepressants.[8] Further studies are needed to examine whether executive dysfunction, white-matter hyperintensities, Axis III comorbidity, chronicity, or undertreatment are factors that moderate lower antidepressant response in late-life MDD patients.

Another possible explanation of lower response rates in the late-life MDD group may be that older patients simply take longer to respond. In a secondary analysis of the effects of study duration on response rates with second-generation antidepressants, Nelson et al[16] found antidepressant and placebo rates of response of 55% and 41%, respectively, among 10- to 12-week trials, compared with 38% and 31%, respectively, in 6- to 8-week trials. Not only were response rates higher in the longer trials, but the reported drug-placebo difference was approximately twice as large. Our present study included the same 10- to 12-week trials as the Nelson et al[16] analysis, as well as 5 additional trials of shorter duration. In the present analyses, drug and placebo response rates were 40.4% and 27.8%, respectively, among the 11 trials of 4 to 8 weeks' duration. These observed response rates were numerically lower than those in the longer trials, although there was little effect on the drug-placebo difference (14.0% vs 12.6%, respectively). Finally, an alternative explanation for our findings that must also be entertained may simply be that the relatively smaller number of older late-life MDD trials (vs all late-life MDD studies), the smaller number of total subjects in these trials, and the fact that the largest such trial was negative are responsible for the absence of positive findings in this subgroup. In the absence of individual patient-level data (linking age with treatment assignment and outcome), it is not possible for us to definitively conclude that antidepressants are more efficacious in younger as opposed to older elderly patients.

Several limitations should be taken into account when interpreting our findings. First, it is important to point out that our dichotomous definitions of age-based populations using age thresholds of 55 and 65 years is somewhat arbitrary (for instance, age 55 was more commonly applied as an inclusion criterion in trials going back more than 20 years and in trials that used older types of antidepressants, while most contemporary regulatory agencies and clinicians consider age 65 as a geriatric cutoff). As a result, it may be that these rather arbitrary divisions may not be the optimal ones to help elucidate the relationship between antidepressant and placebo efficacy in MDD as a function of patient age. A second limitation is that all clinical trials included in the present study involved a number of exclusion criteria and focused on specific pharmacologic interventions (specifically, antidepressants), such that findings of this study may not be generalized to those excluded (ie, patients with bipolar depression or psychotic MDD, patients actively abusing alcohol or drugs, patients with specific medical comorbidities, or patients with serious suicidal ideation), nor to treatment with different modalities (eg, psychotherapy, somatic therapies). Moreover, it is possible that publication bias in the form of the failure to publish equivocal or negative trials may have distorted our findings or inflated our results (since our study focused only on published clinical trials). Another limitation is the relatively small number of clinical trials focusing on the treatment of late-life MDD, in particular in the oldest segment of the population. It should be pointed out, however, that such trials are very challenging to carry out, given that older subjects often present with multiple medical comorbidities and concomitant therapies, which may render recruitment of subjects particularly difficult. A separate limitation is that inclusion of relevant articles was agreed upon by consensus among the study authors. Although this method is usual practice in meta-analyses and is guided by strict inclusion/exclusion criteria, any subjectivity involved in making such a decision has the potential of introducing bias into the study. Finally, due to the nature of our study, our analysis could not take into account other factors that may potentially influence treatment outcome, including Axis I and Axis III comorbidity burden, psychosocial functioning, and social and family status of each individual patient. However, such analyses could be performed only by using patient-level and not study-level data sets.

In conclusion, although the results of the present meta-analysis suggest that antidepressants appear to be efficacious in late-life MDD (including studies utilizing an age threshold of 55 years to define late-life MDD), significant heterogeneity exists. In addition, late-life MDD patients appeared to have significantly lower antidepressant response rates but similar placebo response rates as compared with adult MDD patients. Furthermore, our subanalyses suggested that antidepressants were not more effective than placebo in trials using an age threshold of 65 or 75 years (mean age in these trials was 73.5 years). Although preliminary, these findings raise the possibility that the efficacy of antidepressants may be reduced in the most elderly MDD patients. Factors that may moderate antidepressant response in this select population require further study.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), desvenlafaxine (Pristiq), doxepin (Zonalon, Silenor, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), isocarboxazid (Marplan), milnacipran (Savella), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), protriptyline (Vivactil and others), sertraline (Zoloft and others), tranylcypromine (Parnate and others), trazodone (Oleptro and

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others), trimipramine (Surmontil and others), venlafaxine (Effexor and others).

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Author contributions: All individuals included as authors contributed substantially to the scientific process. All authors made a significant contribution to the study conception, to the design of experimental studies, or to the analysis and interpretation of data. They all participated in drafting and reviewing/revising the manuscript. Finally, they all approved the final version of the manuscript. As the study's principal author, Dr Tedeschini assumes responsibility for the integrity of the work as a whole.

Potential conflicts of interests: **Dr Nelson** has served as a consultant for Bristol-Myers Squibb, Corcept, Covidien, Eli Lilly, Forest, Lundbeck, Medtronics, Merck, Orexigen, Otsuka, Pfizer, and Sanofi-Aventis; has received honoraria from Eli Lilly Global, Otsuka Asia, and Schering-Plough/Merck (Japan and China); has received research support from the National Institute of Mental Health (NIMH) and the Health Resources and Services Administration; has been a member of the speakers bureaus for Bristol-Myers Squibb and Pfizer; has served as an advisor to Bristol-Myers Squibb, Eli Lilly, Labopharm, and Otsuka; and is a stock shareholder of Atossa Genetics. **Dr Papakostas** has served as a consultant for Abbott, AstraZeneca, Brainsway, Bristol-Myers Squibb, Cephalon, Eli Lilly, GlaxoSmithKline, Evotec, Inflabloc, Jazz, Otsuka, Pamlab, Pfizer, Pierre Fabre, Ridge Diagnostics (formerly known as Precision Human Biolaboratories), Shire, and Wyeth; has received honoraria from Abbott, AstraZeneca, Bristol-Myers Squibb, Brainsway, Cephalon, Eli Lilly, Evotec, GlaxoSmithKline, Inflabloc, Jazz, Lundbeck, Otsuka, Pamlab, Pfizer, Pierre Fabre, Ridge Diagnostics, Shire, Titan, and Wyeth; has received research support from Bristol-Myers Squibb, Forest, NIMH, Pamlab, Pfizer, and Ridge Diagnostics; and has served (in the past, but not currently) on the speakers bureaus for Bristol-Myers Squibb and Pfizer. **Drs Tedeschini, Levkovitz**, and **Iovieno** and **Ms Ameral** report no competing interests relative to the subject of this article.

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