

# Efficacy and Safety of Antidepressants for Treatment of Depression in Alzheimer's Disease: A Metaanalysis

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**Objective:** Depression in patients with Alzheimer's disease (AD) is common (15% to 63%) and is associated with significant morbidity and increased mortality. Our objective was to quantitatively summarize the data on the efficacy and safety of antidepressant treatment for depression complicating AD.

**Method:** We performed a metaanalysis of randomized, double-blind, placebo-controlled trials of antidepressants with a database search of the English literature (up to 2006) and a manual search of references in the retrieved articles. We extracted the proportion of subjects who responded and remitted, experienced adverse events (AEs), discontinued treatment due to AEs, or discontinued treatment for any reason. Cognition scores were also extracted.

**Results:** We included 5 studies, which involved 82 subjects treated with antidepressants and 83 subjects who received placebo treatment. Antidepressants were superior to placebo for both treatment response (odds ratio [OR] 2.32; 95% confidence interval [CI], 1.04 to 5.16) and remission of depression (OR 2.75; 95%CI, 1.13 to 6.65). There were no significant differences between the 2 groups for change in cognition (weighted mean difference -0.71, 95%CI, -3.20 to 1.79), overall dropouts (OR 0.70; 95%CI, 0.29 to 1.66) or dropout due to AEs (OR 1.41; 95%CI 0.36 to 5.54). The numbers needed to treat for one additional AD patient to respond to antidepressant treatment were 5 (95%CI, 3 to 59) and 5 (95%CI, 2 to 24) for remission of depression.

**Conclusions:** Antidepressant treatment for depression in AD is efficacious, with rates of discontinuation that are comparable to placebo. Nonetheless, clinicians must be vigilant regarding the potential side effects of antidepressants in this population.

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## Clinical Implications

- Antidepressants are efficacious in the treatment of depression in AD.
- Tolerability of antidepressants in AD appears to be similar to placebo.
- TCAs may be associated with a decline in cognition.

## Limitations

- Antidepressant classes were not compared because of the limited number of published trials in AD.
- Individual AEs could not be analyzed.
- Individual trials were limited by small sample sizes, low medication dosages, differing outcomes of interest, and varying outcomes measures.

**Key Words:** depression, Alzheimer's disease, dementia, antidepressants

Dementia is considered to be one of the most disabling health conditions worldwide. It is anticipated that dementia rates in developed countries will increase by 100% over the next 30 years.<sup>1</sup> Mood and behavioural symptoms are often the first manifestation of the illness and affect up to two-thirds of those with dementia.<sup>2,3</sup> The prevalence of depressive symptoms in AD ranges from 15%<sup>2,4,5</sup> to 63%.<sup>6</sup> It has been suggested that both disorders may coexist owing to a common pathogenetic mechanism.<sup>7</sup> Depression in AD has been associated with increased mortality<sup>8</sup> as well as with significant comorbidities, including reduced quality of life,<sup>9</sup> greater impairments in activities of daily living,<sup>10</sup> earlier admission to and later discharge from long-term care facilities,<sup>11,12</sup> increased likelihood of behavioural disturbances,<sup>13</sup> and increased caregiver burden and prevalence of mood disorders in caregivers.<sup>9</sup> Although suicide attempts have been observed in less than 1% of dementia patients, suicidal ideation, intent, passive death wishes, and feelings that life is not worth living have been reported in 1% to 42% of dementia patients, particularly in those suffering from depression.<sup>14,15</sup>

Depression in dementia is a heterogeneous syndrome, with symptomatology covering the spectrum of subsyndromal illness—from minor depression to full-blown MDD. Assessment must take into account comorbidities, the temporal course of symptoms, and personal and family history of mood disorders.<sup>16</sup> The diagnosis of depression in dementia is challenging, given the patient's often-reduced verbal abilities as well as the inherent difficulty in teasing out the physical and mental status changes that are common in dementia, including emotional dysregulation, apathy, and neurovegetative, cognitive, or personality changes.<sup>16</sup> Recently, provisional diagnostic criteria for depression in AD have been presented<sup>17,18</sup> that tend to mirror the research criteria for minor depressive

disorder in the DMS-IV-TR. These criteria, developed using a consensus process, have not yet been validated.

Treatments of depressive disorders in dementia include psychological interventions, pharmacologic therapies, and ECT. Teri et al have examined behavioural treatments of depression in dementia<sup>19–21</sup> and found them to be effective in reducing depressive symptoms in both patients and caregivers. Retrospective analysis of ECT for the treatment of depression complicating dementia reveals benefits, although with an increased risk of delirium.<sup>22,23</sup>

Metaanalysis is a statistical method used to quantitatively summarize several studies (a minimum of 2) into a single estimate of the magnitude of a particular intervention's effect. To date, one metaanalysis has suggested that there is weak support for the efficacy of antidepressants in the treatment of depression and dementia.<sup>24</sup> We endeavoured to reexamine the RCT literature on the treatment of depression complicating dementia with antidepressants; our approach involved using more recent data and more stringent inclusion criteria. In addition, given suggestions that the NNT and NNH be included in all trials to promote appropriate clinical decision making, we also included these data in our study.<sup>25</sup>

## Method

The population to be studied comprised adults diagnosed with AD according to the diagnostic criteria in the DSM-III,<sup>26</sup> DSM-III-R,<sup>27</sup> and DSM-IV<sup>28</sup> or the criteria of the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association.<sup>29</sup> Acceptable criteria for depression included those according to the DSM-III, -III-R, and -IV criteria for MDD, major depressive episode, dysthymic disorder, and minor depression. Only original reports of double-blind, randomized, placebo-controlled, clinical trials were included.

We searched the English literature, using MEDLINE from January 1966 to June 2006; key words included depression, Alzheimer, and antidepressant. Additional searches also included each of the primary antidepressant classes: SSRIs, TCAs, and monoamine oxidase inhibitors. The Cochrane database was also searched, as were the references of relevant review articles. References in all retrieved articles were also searched for additional relevant studies.

The study design was examined by 2 raters, and a quality rating was calculated, using the Jadad Scale.<sup>30</sup> Next, the results section in each of the relevant articles was examined by 2 raters, and data for each of the following outcome categories were extracted: number of patients responding to treatment, number of patients with remission of depression, cognition score (MMSE<sup>31</sup>) before and after treatment, number reporting AEs, treatment discontinuation (dropout) for any reason, and

### Abbreviations used in this article

AD	Alzheimer's disease
AE	adverse event
CI	confidence interval
DIADS	Depression in Alzheimer's Disease Study
ECT	electroconvulsive therapy
HDRS	Hamilton Depression Rating Scale
MDD	major depressive disorder
MMSE	Mini Mental State Examination
NNH	numbers needed to harm
NNT	numbers needed to treat
OR	odds ratio
RCT	randomized controlled trial
SSRI	serotonin specific reuptake inhibitor
TCA	tricyclic antidepressant

**Table 1 Characteristics of included double-blind, randomized, placebo-controlled trials of antidepressant therapy for the treatment of depression in Alzheimer's disease**

First author, publication year	Drug (average or maximum daily dose)	<i>n</i> (antidepressant, placebo)	Design (duration in weeks)	Depression diagnosis	Dementia diagnosis	Summary of study results	Jadad Quality score
Reifler et al, 1989 <sup>43</sup>	Imipramine (83mg/d)	28 outpatients (13, 15)	Double-blind, parallel RCT, non-ITT analysis (8)	DSM-III MDD HDRS > 14	DSM-III AD MMSE ≤ 25	Imipramine = placebo	3
Petracca et al, 1996 <sup>44</sup>	Clomipramine (100mg/d max)	21 outpatients (11, 10)	Double-blind crossover RCT (6 + 6)	DSM-III-R MDD/ HDRS > 10	Probable AD MMSE > 9	Clomipramine > placebo (at 6 weeks)	3
Magai et al, 2000 <sup>45</sup>	Sertraline (100mg/d max)	31 women in nursing home (17, 14)	Double-blind, parallel RCT (8)	DSM-IV major or minor depression CSDD > 2	Probable AD ("late stage" = stage 6 or 7 on GDS)	Sertraline = placebo	5
Petracca et al, 2001 <sup>46</sup>	Fluoxetine (40mg/d max)	41 outpatients (17, 24)	Double-blind, parallel RCT (6)	DSM-IV major or minor depression HDRS > 13	Probable AD MMSE > 9	Fluoxetine = placebo	3
Lyketsos et al, 2003 <sup>47</sup>	Sertraline (150mg/d max)	44 outpatients (24, 20)	Double-blind, parallel RCT (12)	DSM-IV major depressive episode	Probable AD MMSE > 9	Sertraline > placebo	5

CSDD = Cornell Scale for Depression in Dementia; GDS = Global Deterioration Scale; ITT = intention to treat

dropout due to AEs. Response was defined as a 50% or greater reduction in a standardized measure for depression. Remission was defined as a score of < 8 on the 17-item HDRS. Other definitions of depression remission or response were also considered if they were deemed clinically valid and (or) relevant. AEs were defined in this analysis as any AE reported by the original study authors that occurred during treatment. Cognitive change data were obtained by subtracting mean MMSE scores before treatment from the mean score after treatment. To obtain a standard deviation for cognitive change, the larger of the 2 standard deviations for the treatment and control group cognition scores was used to determine the most conservative estimate of treatment effect. Any discrepancies were resolved through consensus discussion among the reviewers.

We used Review Manager Version 4.2 (Oxford [GB]: Cochrane Collaboration Software; 2004) for analysis. For dichotomous outcomes of interest, pooled ORs and 95% CIs were calculated with a random effects model. For continuous data (cognition change after treatment), a weighted mean difference method was used. Heterogeneity was tested for all combined results by means of chi-square analysis, and  $I^2$  was calculated to determine the impact of heterogeneity.<sup>32</sup>

Publication bias was assessed where there were 5 or more studies using funnel plots.

The NNT and NNH were calculated according to the method outlined by Cook and Sackett.<sup>33</sup> Altman's method of describing CIs<sup>34</sup> was used when the difference between treatment groups was not statistically significant.

## Results

Of the 13 potentially relevant RCTs retrieved in the literature searches, 8 were excluded for the following reasons: medication not available in North America<sup>35</sup>; study population did not have depression<sup>36</sup>; only a portion of the study population had dementia and were not explicitly identified in the study<sup>38,39</sup>; or study data were only presented as *P* values.<sup>40</sup> Raw study data were requested from several studies' authors and sites and (or) drug manufacturers<sup>38-40</sup>; however, this information was not received. Two studies were not included<sup>41,42</sup> because they were head-to-head studies that were not placebo-controlled. Ultimately, 5 studies met the inclusion criteria<sup>43-47</sup> (Table 1), and all had Jadad Quality scores of 3 or greater. The included studies examined the use of antidepressants in a total of 82 subjects and placebo treatment in 83 subjects. None of the 5 included studies reported

**Table 2 Summary of comparative outcomes (data extracted from included studies and pooled)**

Outcome	<i>n</i> (antidepressant, placebo)	Effect estimate (95%CI)	Heterogeneity: $\chi^2$ ( <i>P</i> value)	Inconsistency: $\chi^2$ (%)	NNT or NNH (95%CI)
Response	116 (58, 58)	OR 2.32 (1.04 to 5.16)	1.36 (0.51)	0	5 (3 to 59)
Remission	106 (52, 54)	OR 2.75 (1.13 to 6.65)	2.14 (0.34)	6.5	5 (2 to 24)
Cognition	113 (54, 59)	WMD -0.71 (-3.20 to 1.79)	0.55 (0.76)	0	na
Dropout	165 (82, 83)	OR 0.70 (0.29 to 1.66)	1.61 (0.81)	0	21 (6 to $\infty$ )
Dropout owing to adverse events	137 (69, 68)	OR 1.41 (0.36 to 5.54)	0.62 (0.89)	0	36 (9 to $\infty$ )

WMD = weighted mean difference; na = not applicable

data for all 6 outcomes of interest (depression remission, response, AEs, dropout, dropout due to AEs, and change in cognition).

### *Antidepressant Efficacy*

The proportion of subjects who had a reduction in depressive symptoms (responders) was extractable from 3 of the studies (Figure 1A). The overall OR for response was 2.32 (95%CI, 1.04 to 5.16), indicating statistically significant superiority of antidepressant over placebo treatment (Table 2).

The proportion of subjects experiencing a remission of depressive symptoms was extractable from 3 studies (Figure 1B). The overall OR for remission rate was 2.75 (95%CI, 1.13 to 6.65), which favoured the group treated with antidepressants (Table 2).

### *Cognitive Change*

Change in cognition, measured with the MMSE pre- and posttreatment, was reported in 3 of the included studies (Figure 2). There was no statistically significant change in cognition between the antidepressant- and placebo-treated groups pre- and posttreatment (weighted mean difference -0.71 [95%CI, -3.20 to 1.79]) (Table 2).

### *Safety*

The proportion of subjects who dropped out for any reason was extractable from all 5 studies included in our metaanalysis (Figure 3A), and dropout rates due to AEs were extractable from 4 of the included studies (Figure 3B). There was no statistically significant difference between the groups treated with placebo or antidepressant in terms of dropout (OR 0.70; 95%CI, 0.29 to 1.66) or dropout due to AEs (OR 1.41, 95%CI, 0.36 to 5.54) (Table 2). AE data for individual symptoms could not be combined by metaanalysis because

only 2 of the included studies<sup>44,45</sup> included raw data on this outcome.

### *Heterogeneity and Publication Bias*

For all outcomes, there was no statistically significant heterogeneity between the studies (all  $I^2 < 20\%$ ) (Table 2) and no evidence of publication bias with regard to funnel plots.

### *Numbers Needed to Treat or Harm*

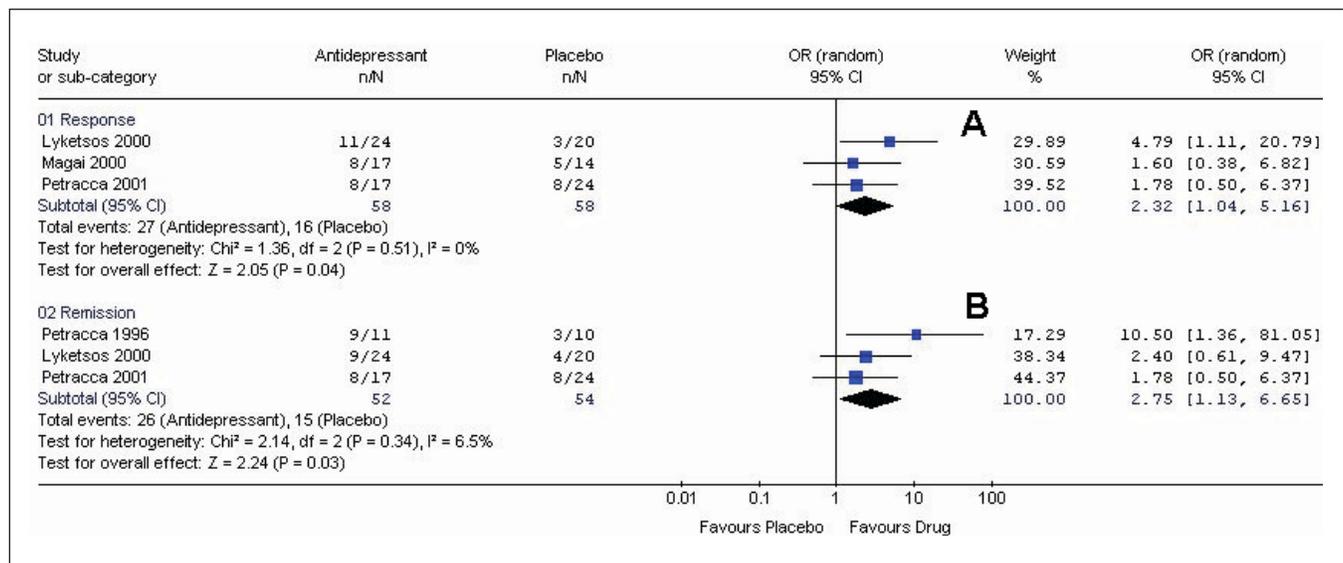
According to the included studies, the number of AD patients with depression who needed to be treated with an antidepressant for one additional patient to demonstrate a response to treatment was determined to be 5 (95%CI, 3 to 59). For full remission of depressive symptoms, the NNT was 5 (95%CI, 2 to 24). For study dropout, for any reason, the NNH one additional patient was 21 and was not statistically significant because the 95%CI crossed zero (95%CI, 6 to  $\infty$ ). Similarly, the NNH for dropout owing to AEs was not statistically significant (NNH 36; 95%CI, 9 to  $\infty$ ) (Table 2).

### **Discussion**

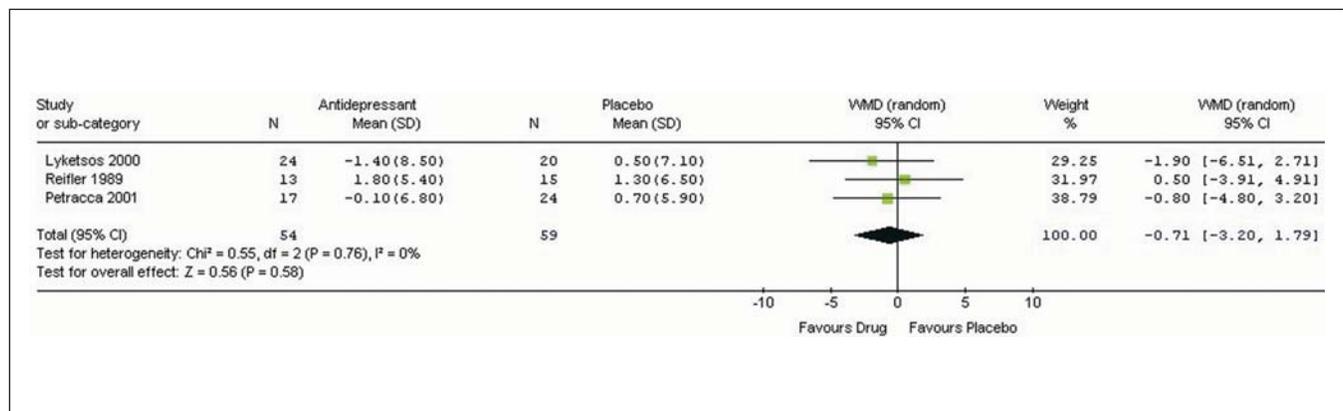
Depression is commonly seen in AD and results in significant morbidity as well as mortality. This metaanalysis of the treatment of depression in AD patients with antidepressants demonstrates a statistically significant reduction in depressive symptoms (that is, antidepressant response) as well as remission of depressive symptoms.

Our report includes NNTs, which are a clinically relevant format for presenting statistical information about an intervention. The NNT of 5 for one additional patient to achieve remission of depressive symptoms in AD is comparable to the NNT of between 1 and 8 estimated for the treatment of depression in cognitively intact elderly individuals.<sup>41</sup> Similarly, the NNTs are 3 to 5 for response in dysthymia in a younger adult

**Figure 1 Response to treatment of depressive symptoms in Alzheimer’s disease patients: antidepressant compared with placebo. Panel A, response; Panel B, remission**



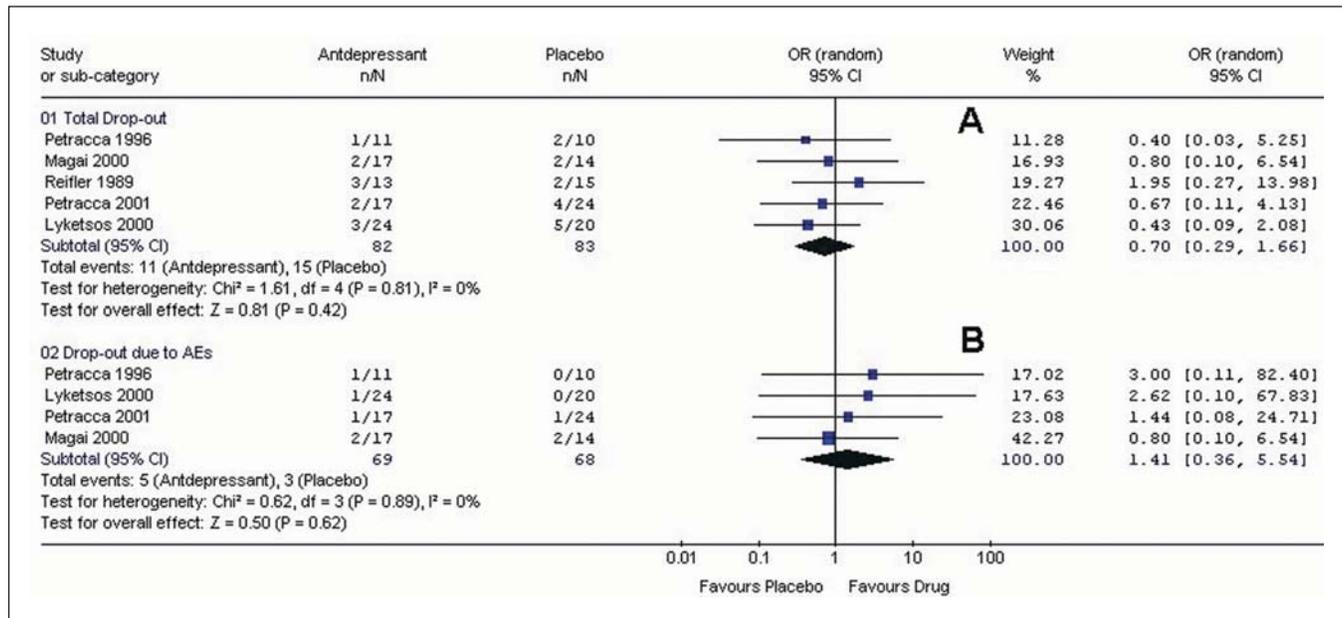
**Figure 2 Change in cognition following treatment of depression: antidepressant compared with placebo**



population<sup>48</sup> and 4 for improvement of depression in medical illness.<sup>49</sup> Thus the NNT in this study is similar to those found for antidepressants used in other populations. With regard to safety data, we were not able to complete a metaanalysis of specific AE data because this outcome was not explicitly reported in all studies. Rates of dropout for any reason, as well as dropout due to AEs, did not differ significantly between antidepressant and placebo. NNHs for dropout data produced wide CIs, suggesting inadequate sample size to demonstrate risks associated with antidepressant use in patients with dementia. Certainly, antidepressants are not without side effects. Unfortunately, studies of AEs associated with antidepressant use in the elderly do not customarily include patients with dementia. It is unclear whether a similar risk is present in dementia patients because the small number of

subjects in these trials—even when pooled—makes it more difficult to demonstrate the existence of AEs. Given their concomitant physical and cognitive frailty, this subpopulation may be more susceptible to adverse effects, including gastrointestinal upset, headache, orthostatic hypotension, falls, and, more rarely, hyponatremia and increased suicidal ideation.<sup>50,51</sup> Clinicians must be vigilant for any evidence of AE emergence that may be evinced by behavioural changes in dementia patients, as they may not be able to communicate them verbally. Antidepressant prescription in dementia patients should always be made using the familiar adage “start low and go slow.”

Due to the larger cumulative number of included studies and statistical techniques used in metaanalysis, it is not uncommon for the final conclusion of the metaanalysis to vary from

**Figure 3 All-cause dropouts (Panel A) and dropouts due to adverse events (Panel B): antidepressants compared with placebo**

that of the included individual studies. When the 5 included studies were examined individually, only 2 showed antidepressant medication (clomipramine and sertraline) to be more effective than placebo.<sup>44,47</sup> One showed equivalence of antidepressant (sertraline) and placebo in advanced dementia.<sup>45</sup> The 2 remaining studies, involving patients with mild-to-severe dementia, also demonstrated no difference between placebo and antidepressant (fluoxetine and clomipramine) in primary efficacy measures.<sup>43,46</sup> We are unable to comment on superiority of efficacy between classes of antidepressants (that is, TCAs, compared with SSRIs) owing to the small number of studies included in the metaanalysis. However, it is notable that significant declines in cognition were measured in the 2 studies involving TCAs,<sup>43,44</sup> and thus caution is advised when prescribing this class of medication to those with dementia. Raw data were not obtainable for one positive study of moclobemide that involved a substantial number of subjects<sup>40</sup>; although this omission is unfortunate, moclobemide is not available in the United States and is used relatively infrequently in Canada. Newer antidepressant medications, including bupropion, mirtazapine, and venlafaxine, could also not be included in the current metaanalysis because of a lack of published RCTs on this population.

The results of this metaanalysis are somewhat different than those of Bains et al.<sup>24</sup> While both metaanalyses included Reifler et al.<sup>43</sup> and Petracca et al.,<sup>44</sup> Bains et al.<sup>24</sup> considered a

preliminary report of DIADS ( $n = 22$ ), whereas we included the final DIADS publication ( $n = 44$ ).<sup>47</sup> In addition, from the numbers reported in the prior metaanalysis by Bains et al, it appears that some nondepressed patients with dementia were also included. The current metaanalysis included only the 28 patients in the 1989 Reifler study<sup>43</sup> reported to have dementia as well as depression.

It is important to point out that publication bias can be an important limitation to any metaanalysis. McAuley and colleagues<sup>52</sup> have suggested that the exclusion of "grey literature" can overestimate treatment effect by as much as 15%. If Rosenthal's equation is used to determine the number of negative studies filed away (the "file drawer problem") to nullify the results of this metaanalysis, there would have to be 11 such studies in existence.<sup>53</sup>

Another limitation of this metaanalysis is that only a small number of studies have been performed. Further, each of the included studies was limited by several of the following factors: small sample size, low medication dosages, differing outcomes of interest, and varying outcomes measures. Whereas several researchers have suggested that between 12 and 16 weeks are required to demonstrate an optimal treatment effect for antidepressants in older adults, the duration of the studies included in the present metaanalysis ranged from 6 to 12 weeks.<sup>54,55</sup> Another complicating factor was the heterogeneous definitions of depression and dementia in the included studies. This could perhaps be remedied in future

studies on the treatment of depression in AD by using the recently proposed standardized depression measures in AD diagnostic criteria.<sup>17,18</sup>

## Conclusions

The results of this metaanalysis indicate that antidepressant therapy in AD is efficacious, compared with placebo therapy. In addition, a small number of patients need to be treated to achieve response and (or) remission of depressive symptoms. The reader is cautioned, however, that this conclusion is based on a small number of published studies and that, although AE data are limited, clinicians must continue to be vigilant regarding the emergence of side effects in dementia patients being started on antidepressant medications. More large-scale RCTs are needed to clarify the benefits, and particularly the risks, of antidepressant therapy for the rapidly growing segment of our population who suffer from AD.

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## Résumé : Efficacité et innocuité des antidépresseurs pour le traitement de la dépression dans la maladie d'Alzheimer : une méta-analyse

**Objectif :** La dépression chez les patients souffrant de la maladie d'Alzheimer (MA) est répandue (15 % à 63 %) et est associée avec une morbidité significative et une mortalité accrue. Notre objectif était de résumer quantitativement les données sur l'efficacité et l'innocuité du traitement aux antidépresseurs pour la dépression compliquant la MA.

**Méthode :** Nous avons effectué une méta-analyse d'essais randomisés, à double insu, contrôlés contre placebo d'antidépresseurs au moyen d'une recherche de bases de données de la documentation en anglais (jusqu'en 2006) et d'une recherche manuelle des bibliographies des articles trouvés. Nous avons extrait la proportion de sujets qui répondaient et se rétablissaient, qui avaient des réactions adverses (RA), qui ont cessé le traitement à cause des RA, ou qui ont cessé le traitement pour toute autre raison. Les scores de cognition ont aussi été extraits.

**Résultats :** Nous avons inclus 5 études, regroupant 82 sujets traités aux antidépresseurs et 83 sujets qui ont reçu un traitement au placebo. Les antidépresseurs étaient supérieurs au placebo tant pour la réponse au traitement (odds ratio [OR] 2,32; 95 % intervalle de confiance [IC], 1,04 à 5,16) que pour la rémission de la dépression (OR 2,75; 95 % IC, 1,13 à 6,65). Il n'y avait pas de différences significatives entre les 2 groupes en ce qui concerne le changement de cognition (différence moyenne pondérée -0,71; 95 % IC, -3,20 à 1,79), abandons globaux (OR 0,70; 95 % IC, 0,29 à 1,66) ou abandons à cause des RA (OR 1,41; 95 % IC, 0,36 à 5,54). Les nombres qu'il fallait traiter pour qu'un patient additionnel de la MA réponde au traitement aux antidépresseurs étaient 5 (95 % IC, 3 à 59) et 5 (95 % IC, 2 à 24) pour la rémission de la dépression.

**Conclusions :** Le traitement aux antidépresseurs pour la dépression dans la MA est efficace, et les taux de cessation sont comparables au placebo. Néanmoins, les cliniciens doivent être vigilants en ce qui concerne les effets secondaires potentiels des antidépresseurs dans cette population.