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Review

Efficacy of treatment in older depressed patients: A systematic review and meta-analysis of double-blind randomized controlled trials with antidepressants

Rob M. Kok [a,*], Willem A. Nolen [b], Thea J. Heeren [c]

[a] Department of Old Age Psychiatry, Parnassia Psychiatric Institute, The Hague, The Netherlands
[b] Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[c] Symfora Group Centers of Mental Health Care, Amersfoort, The Netherlands

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ABSTRACT

Background: This systematic review evaluated all published double-blind, randomized controlled antidepressant trials (RCTs) of acute phase treatment of older depressed patients.
Methods: Meta-analyses were conducted in 51 double-blind RCTs of antidepressants in older patients. The results were also compared with 29 double-blind RCTs that did not produce extractable data to enter the meta-analysis.
Results: All classes of antidepressant (TCA's, SSRIs and other antidepressants) were more effective than placebo in achieving response. In achieving remission however, only pooling all 3 classes of antidepressants together showed a statistically significant difference from placebo. No differences were found in remission or response rates between classes of antidepressants. TCAs were also equally effective compared with SSRIs in achieving response in more severely depressed patients. The numbers needed to treat (NNT) were 14.4 (95% CI 8.3–50) for one additional remission to antidepressants compared with placebo and 6.7 (95% CI 4.8–10) for response. The results of the double-blind RCTs that did not produce extractable data to enter the meta-analysis were in concordance with the RCTs that were included in the meta-analysis.
Limitations: Only 4 RCTs were found that have not been published. Few studies have focused on severely depressed older people.
Conclusions: Antidepressant treatment in older depressed patients is efficacious. We could not demonstrate differences in effectiveness between different classes of antidepressants; this was also the case in more severely depressed patients.

Contents

* Corresponding author at: Parnassia Psychiatric Institute, Department of old age psychiatry, Mangostraat 1, 2552 KS The Hague, The Netherlands. Tel.: +31 88 3575252; fax: +31 88 3584166.
E-mail address: r.kok@parnassia.nl (R.M. Kok).

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1. Introduction

Many randomized controlled trials (RCTs) in depressed older patients have been published and the vast majority of these reported significantly greater efficacy of antidepressants than placebo (Taylor and Doraiswamy, 2004). Combining the results of these individual studies in a systematic review and meta-analysis has many advantages. Summarizing the results of individual studies can provide more precise estimates of the effect of treatment and overcomes the difficulty that many studies are underpowered. Moreover, subgroup analysis may answer important questions such as possible differences in efficacy between antidepressant classes in older patients. In adult patients, subgroup analysis has found a greater efficacy of tricyclic antidepressants (TCAs) compared with selective serotonin reuptake inhibitors (SSRIs) among inpatients but no difference in efficacy between more severely and less severely depressed patients (Anderson, 2000). The question whether TCAs are more effective than SSRIs in psychiatric inpatients or in severely depressed patients has not been addressed in systematic reviews among older patients.

In one of the first reviews of the efficacy of antidepressants in depression in the older patients, published in 1988, only 12 double-blind studies were found (Gerson et al., 1988). The conclusions were that antidepressants are clearly superior to placebo, and that older patients are just as likely as younger patients to go into remission given appropriate treatment. All reviews of placebo-controlled studies in older depressed patients published since then, also concluded that antidepressants are more effective than placebo (McCusker et al., 1998; Mittmann et al., 1997; Nelson et al., 2008; Taylor and Doraiswamy, 2004; Williams et al., 2000a; Wilson et al., 2001). These reviews also suggested that efficacy of antidepressants in older patients is comparable with efficacy in adult patients. Most of the reviews did not find a difference between classes of antidepressants in older patients, including a more recent review specifically aimed at comparing single- versus dual-action antidepressants (Mukai and Tampi, 2009). One review found a smaller Numbers-Needed-to-Treat (NNT) in the placebo controlled RCTs with TCAs (NNT 3.97, 95% confidence interval (CI) = 3.88–4.05) than with SSRIs (8.45; 95% CI = 8.38–8.53) (Wilson et al., 2001). However, in studies directly comparing TCAs with SSRIs, no differences in efficacy are found.

Reviews may also have disadvantages. The number of included RCTs in the reviews mentioned above ranges from 6 to 32, suggesting that there are not many studies in the older patients. However, a closer look at the inclusion and exclusion criteria of all these reviews reveals that only a minority of published studies was included in these reviews. Although this may increase the internal validity of the review, this usually limits the external validity (generalizability) of the results. Another example is the need to have comparable, quantitative data. Both Cochrane reviews in non-demented elderly excluded many studies because they did not publish extractable data on number of patients with remission or response, necessary for a meta-analysis (Mottram et al., 2006; Wilson et al., 2001). However, this exclusion criterion is somewhat arbitrary and moreover, these studies may contain important additional information concerning the differential efficacy of antidepressants. Finally, some reviews included studies that were not double-blind or did not have a blinded outcome assessor, which are both important qualitative factors to prevent bias.

Our aim was to provide a systematic review of all acute phase double-blind RCTs of antidepressants in older depressed patients without dementia. We included studies using outcome criteria that differ from the primary or secondary outcome criteria, in order to compare these results with studies that could be pooled into the meta-analysis.

Our questions were: (1) do the various classes of antidepressants (TCAs, SSRIs and other antidepressants) have different efficacy rates when compared to placebo; (2) are there differences in efficacy between the various classes of antidepressants when compared with each other; (3) are there differences between the various classes among subgroups of older depressed patients (e.g. in inpatients, severely depressed patients).

In addition to proving again that the various classes of antidepressants (TCAs, SSRIs as well as other antidepressants) are effective in non-demented older depressed patients and that efficacy would not be different between these classes when compared to each other, we hypothesized a priori that TCAs would be more effective than SSRIs among psychiatric inpatients and possibly also among the more severely depressed patients.

2. Methods

This systematic review aimed to include all published double-blind RCTs with antidepressants in the acute phase treatment of unipolar depression in patients with a minimum age of at least 55 years, or described as elderly, senile, geriatric or older adults. Because there are important differences between countries in registering drugs as antidepressants, we have used the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization as an internationally accepted standard of defining whether a drug was an antidepressant or not (http://www.whocc.no). Patients could be diagnosed as suffering from major depressive disorder, dysthymia, minor depression, subclinical or

subthreshold depression or non-specified depression, but we have repeated the most important analyses with studies limited to major depression. Trials not using any criteria for diagnosing depression were excluded. When a study did allow both unipolar and bipolar depressed patients (and the analysis did not provide data of the unipolar group), the study was only included when ≤20% of the patients had a bipolar depression. Trials aimed to include only patients suffering from concomitant physical illness (e.g. post stroke patients) were excluded.

Additional quality criteria to enter the meta-analysis were the use of a standardized rating instrument to assess efficacy (see below for outcome measures), and the possibility to perform an intention to treat (ITT) analysis based on inclusion of all patients who were randomized.

We searched the literature using PubMed, EMBASE and the Cochrane Controlled Trials Register up to Jan 2012 with age limits (Middle Aged, Aged, 80 and over) without any language restriction. The following medical subject headings (MeSH) were used: (randomized) controlled trial, depression and related terms, antidepressant, TCA, SSRI, monoamine oxidase inhibitor (MAOI), second generation antidepressant, atypical antidepressant. All individual, non-proprietary drug names were also used.

In addition, manual cross referencing of trials and reviews in older patients was used to identify potential RCTs of interest, including posters and oral presentations. The three reviews which explicitly mention RCTs that were excluded, including 2 Cochrane reviews that had extensively searched The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register, were hand searched for studies of interest for our review (Mittmann et al., 1997; Mottram et al., 2006; Wilson et al., 2001). Unpublished studies were already identified in other reviews after extensive searches (Katona and Livingston, 2002; Mottram et al., 2006; Wilson et al., 2001). In case of missing data, authors and sponsors were contacted.

Grouping of antidepressants by class of drug varies across reviews. To be consistent with the meta-analysis of Anderson (2000), we classified the antidepressants as follows;

Tricyclic and related antidepressants: nortriptyline, amitriptyline, clomipramine, desipramine, dosulepine, dothiepine, doxepine, imipramine, lofepramine, maprotiline, nomifensine, trimipramine.

SSRIs; citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, zimeldine.

Consequently we grouped all other compounds among the heterogenous group of 'other antidepressants': bupropion, duloxetine, mianserine, medifoxam, milnacipran, minaprine, mirtazapine, moclobemide, nefazodone, phenelzine, reboxetine, tianeptine, trazodone, venlafaxine, viloxazine.

The primary outcome of the meta-analyses was remission, dichotomized according to a final score lower than a cut-off on the Hamilton Depression Rating Scale (HAM-D, the cut-off was dependent on the version, but typically ≤7 or ≤10; Hamilton, 1960), or on the Montgomery Åsberg Depression Rating Scale (MADRS, most frequently used cut-off ≤12; Montgomery and Åsberg, 1979). Secondary outcomes were response (defined as a ≥50% decrease on the HAM-D, MADRS or other depression rating scale or as a Clinical Global Impressions-Improvement Scale (CGI-I) score of 1 or 2 (very much or much improved)) and decrease on a depression rating scale if efficacy was also reported as a continuous outcome. For the ITT meta-analyses, all patients not completing the trial were considered non-remitters and non-responders. Data were extracted from the studies by 2 independent reviewers, who settled any differences by agreement (RK and CB).

In case of studies where 2 antidepressants were compared with placebo and both antidepressants were within the same class of antidepressant, e.g. two SSRIs versus placebo, we combined the results from both SSRIs. If two different classes of antidepressant were compared with placebo, we have split the placebo group into half in order to prevent the placebo-patients to be counted twice.

Trial duration was not used as a variable to control for in our analyses, as two reviews have shown that duration did not affect efficacy in the elderly (Sneed et al., 2008; Wilson et al., 2001). Trials with greater mean baseline severity were separated from trials with lower mean baseline severity on the MADRS or HAM-D, using a median split according to Anderson (2000).

We used Review Manager Version 4.2 (Oxford, GB: Cochrane Collaboration Software 2004) for analysis. A fixed effect model was used for calculating pooled Odd Ratios (OR) and 95% Confidence Intervals in case of dichotomous outcomes. If substantial heterogeneity was found ($I^2 > 30\%$), random effects models were used for analyses. For continuous outcomes, a weighted mean difference method (WMD) was used. The NNT were calculated with Review Manager using Risk Differences as outcome, the confidence intervals were calculated according to Altman (1998).

3. Results

A total of 155 potentially relevant, double-blind RCTs were identified and screened for retrieval. The flow chart of selection of RCTs is presented in Fig. 1.

Twenty-one RCTs were excluded because they did not use antidepressants but acetyl-L-carnitine (Bella et al., 1990; Gecele et al., 1991), ACTH 4–9 analog (Frederiksen et al., 1985), adinazolam (Feighner et al., 1990), brofaromine (Moller and Volz, 1993), diclofensine (Gentili et al., 1984; Jansen et al., 1982), flupenthixol (Hostmaelingen et al., 1989), lithium (Wilkinson et al., 2002), methylphenidate (Wallace et al., 1995), nimodipine (Taragano et al., 2001, 2005), perphenazine (Meyers et al., 2001), procaine (Aslan et al., 1986; Bălăceanu-Stolnici et al., 1996), rolipram (Behnke et al., 1992), St. John's Wort (Harrer et al., 1999), sulpiride (Kivelä and Lehtomäki, 1987), tryptophan (Cooper and Datta, 1980; Rousseau, 1987), or combined fluphenazine/nortriptyline (Brodie et al., 1975).

Eighteen RCTs were excluded because no diagnostic criteria were used to diagnose depression (Branconnier et al., 1982, 1983; Burrows et al., 2002; Fairweather et al., 1993; Ghose, 1997; Goldstein et al., 1982; Kane et al., 1983; Kernohan et al., 1967; Kretschmar, 1979; Lakshmanan et al.,

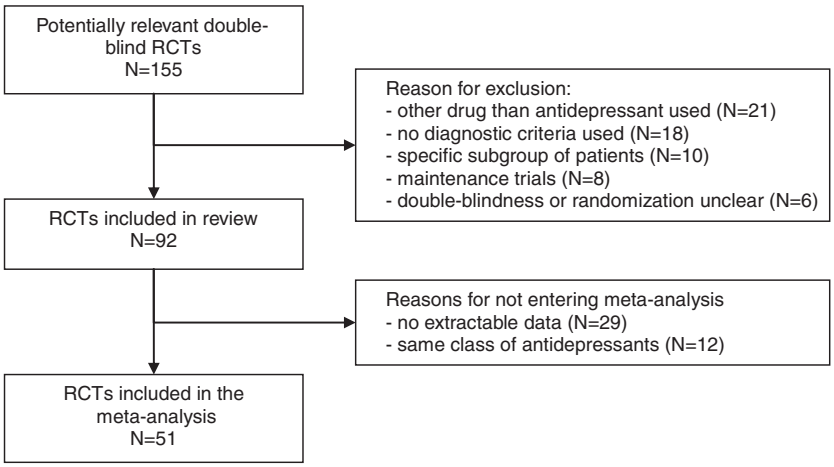

Fig. 1. Flow diagram of RCTs.

1986; Malsch et al., 1996; Middleton, 1975; Nugent, 1979; Passeri, 1987; Scardigli and Jans, 1982; Shapiro et al., 1960; Tan et al., 1994; Von Knorring, 1980).

RCTs aimed at specific subgroups were not included to produce more homogeneous results: 7 studies including a majority of patients with dementia (Cunha et al., 2007; Lyketsos et al., 2003; Magai et al., 2000; Passeri et al., 1993; Petracca et al., 1996, 2001; Rosenberg et al., 2010), two in patients with dysthymia or minor depression (Devanand et al., 2005; Williams et al., 2000b) and one in patients with treatment-resistant depression (Sunderland et al., 1994). The only RCT in patients with a psychotic depression was a continuation trial already excluded because patients using nortriptyline were randomized to perphenazine or placebo (Meyers et al., 2001).

Studies into maintenance treatment (8 studies: Alexopoulos et al., 2000; Georgotas et al., 1989; Gorwood et al., 2007; Klysner et al., 2002; Old Age Depression Interest Group, 1993; Reynolds et al., 1999a, 1999b; Reynolds et al., 2006; Wilson et al., 2003) were also excluded.

Six unpublished studies of potential interest, in part identified in other reviews (Katona and Livingston, 2002; Mottram et al., 2006) were excluded because it was not possible to determine whether these studies were randomized and double-blind (Cassano et al., 1998; Dong-Ming et al., 2006; Giakis et al., 1993; Elly Lilly, 1993; Mingjun, 2007; Tourigny-Rivard et al., 1996). We were able to find the vast majority of studies identified as unpublished in previous reviews (Bondareff et al., 2000; Branconnier et al., 1982; Forlenza et al., 2001; Guelfi et al., 1999; Hoyberg et al., 1996; Katona et al., 1998; Newhouse et al., 2000; Roose et al., 2004; Schatzberg and Roose, 2006; Schatzberg et al., 2002; Smeraldi et al., 1998; Trick et al., 2004; Wehmeier et al., 2005).

Fifty-one of the remaining 92 RCTs were included in at least one of the meta-analyses. Twenty-nine RCTs could not be included in the meta-analysis because they did not produce the number of patients achieving response or remission criteria as defined in the method section. Twelve other RCTs could not be included because 2 antidepressants from the same class were compared with each other (Bayer et al., 1989; Brion et al., 1996; Cassano et al., 2002; De Vanna et al., 1990; Fairbairn et al., 1989; Finkel et al., 1999; Geretsegger et al., 1994; Gwirtsman et al., 1983; Nair et al., 1993; Newhouse et al., 2000; Rossini et al., 2005; Streim et al., 2000). Only one RCT that allowed patients with bipolar depression (6 out of 241 patients) was included in the meta-analysis (Cohn et al., 1990).

3.1. Efficacy of antidepressants: placebo-controlled RCTs

Our first question concerned the short term efficacy of different classes of antidepressants as found in placebo-controlled trials. The meta-analyses with remission rates and with response rates are presented in Figs. 2 and 3. A funnel plot failed to demonstrate clear evidence of missing or unpublished negative studies. If all antidepressants are combined, the difference in achieving remission is statistically significantly different from placebo (OR 1.36; 95% CI 1.07–1.73) with a NNT of 14.4 (95% CI 8.3–50). The difference in achieving a response is also statistically significant different from placebo (OR 1.78 with 95% CI 1.42–2.24) with a NNT of 6.7 (95% CI 4.8–10). Limiting these analyses to studies that only included patients with major depression resulted in non-significant changes in ORs.

TCAs were compared with placebo in 12 RCTs of which only 3 compared remission rates with no statistically significant difference (OR (fixed) 2.11, 95% CI 0.93–4.78, Gerner et al., 1980; Nair et al., 1995; Reynolds et al., 1999a). Seven RCTs presented response rates as defined above (≥50% decrease on HAM-D or MADRS ($n=3$) or a CGI score of 1 or 2 ($n=4$)) and could be entered into a meta-analysis (Georgotas et al., 1986; Katz et al., 1990; Merideth et al., 1984; Nair et al., 1995; Schweizer et al., 1998; Wakelin, 1986; Weissman et al., 1992). The difference is statistically significant (OR (fixed) 2.63, 95% CI 1.52–4.55) and the NNT for response is 4.2 (95% CI = 2.8–7.7). Two out of 3 RCTs that did not produce extractable efficacy data necessary to be included in the meta-analysis found a significant difference in favor of the TCA compared with placebo (Cohn et al., 1984; Jansen and Siegfried, 1984; Sloane et al., 1985).

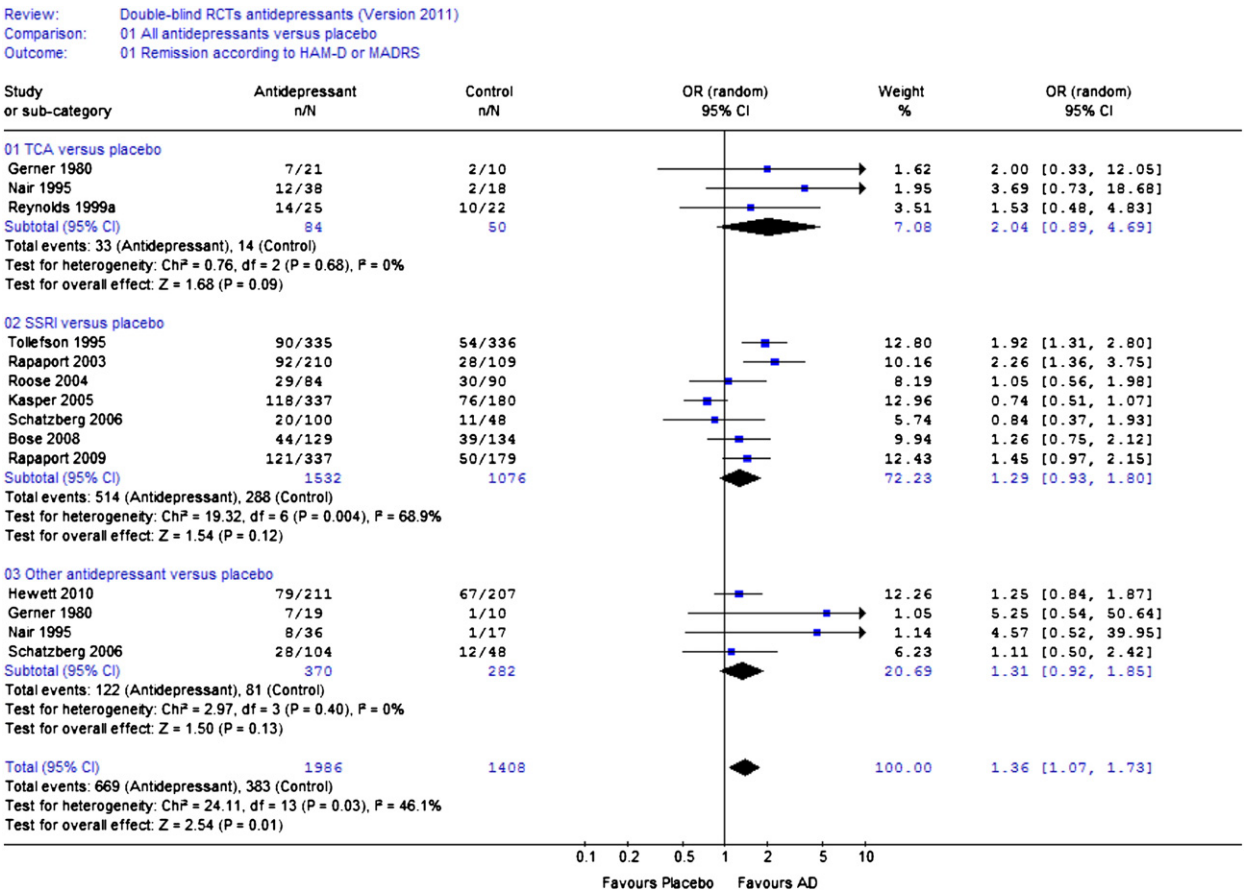

Fig. 2. Remission on HAM-D, MADRS or CGI in TCAs, SSRIs and other antidepressants compared with placebo.

Not enough studies presented continuous outcome data to calculate a Weighted Mean Difference.

SSRIs were compared with placebo in 11 RCTs. Seven of these studies presented remission rates (Fig. 2) (Bose et al., 2008; Kasper et al., 2005; Rapaport et al., 2003, 2009; Roose et al., 2004; Schatzberg and Roose, 2006; Tollefson et al., 1995). The difference was statistically not significant (OR 1.29; 95% CI = 0.93–1.80). Ten RCTs comparing SSRIs with placebo presented response rates on HAM-D, MADRS or CGI (Fig. 3) (Bose et al., 2008; Evans et al., 1997; Kasper et al., 2005; Nyth et al., 1992; Rapaport et al., 2003, 2009; Roose et al., 2004; Schneider et al., 2003; Tollefson et al., 1995; Wakelin, 1986). The difference is statistically significant (OR 1.61, 95% CI 1.18–2.20) and the NNT for response is 10 (95% CI = 6.7–20). Adding the results of one study we previously excluded because it had not been published (Elly Lilly, 1993, results mentioned in Katona and Livingston, 2002) did not have a significant change in the OR.

The change in HAM-D score was also significantly different in SSRIs compared with placebo (5 studies with WMD 1.2; 95% CI = 0.3–2.1) (Bose et al., 2008; Rapaport et al., 2003; Roose et al., 2004; Schneider et al., 2003; Tollefson et al., 1995).

Finally 10 RCTs compared another antidepressant with placebo. Only 4 studies compared remission rates of another antidepressant (trazodone, moclebemide, venlafaxine and bupropion, respectively) with placebo, with no significant differences (OR (fixed) 1.34; 95% CI 0.95–1.89) (Gerner et al., 1980; Hewett et al., 2010; Nair et al., 1995; Schatzberg and Roose, 2006). Six studies reported response rates resulting in a significant difference (OR 1.83, 95% CI 1.21–2.78) and a NNT of 3.5 (95% CI = 3.5–14.3) (De Leo et al., 1984; Georgotas et al., 1986; Halikas, 1995; Hewett et al., 2010; Nair et al., 1995; Raskin et al., 2007). Both RCTs that did not produce extractable efficacy data found a significant difference in favor of another antidepressant compared with placebo (Meignan-Debray et al., 1990; Parnetti et al., 1991). Not enough studies presented continuous outcome data to calculate a Weighted Mean Difference.

3.2. Different efficacy between classes of antidepressants

Our next question concerned possible differences in efficacy between classes of antidepressants.

In the 16 RCTs that used our primary outcome criterion of remission, no significant difference could be demonstrated between treatment with a TCA compared neither with SSRIs (five RCTs; Forlenza et al., 2001; Guillibert et al., 1989; Kyle et al., 1998; Limosin et al., 2006; Wehmeier et al., 2005) nor with other antidepressants (7 RCTs; Georgotas et al., 1986;

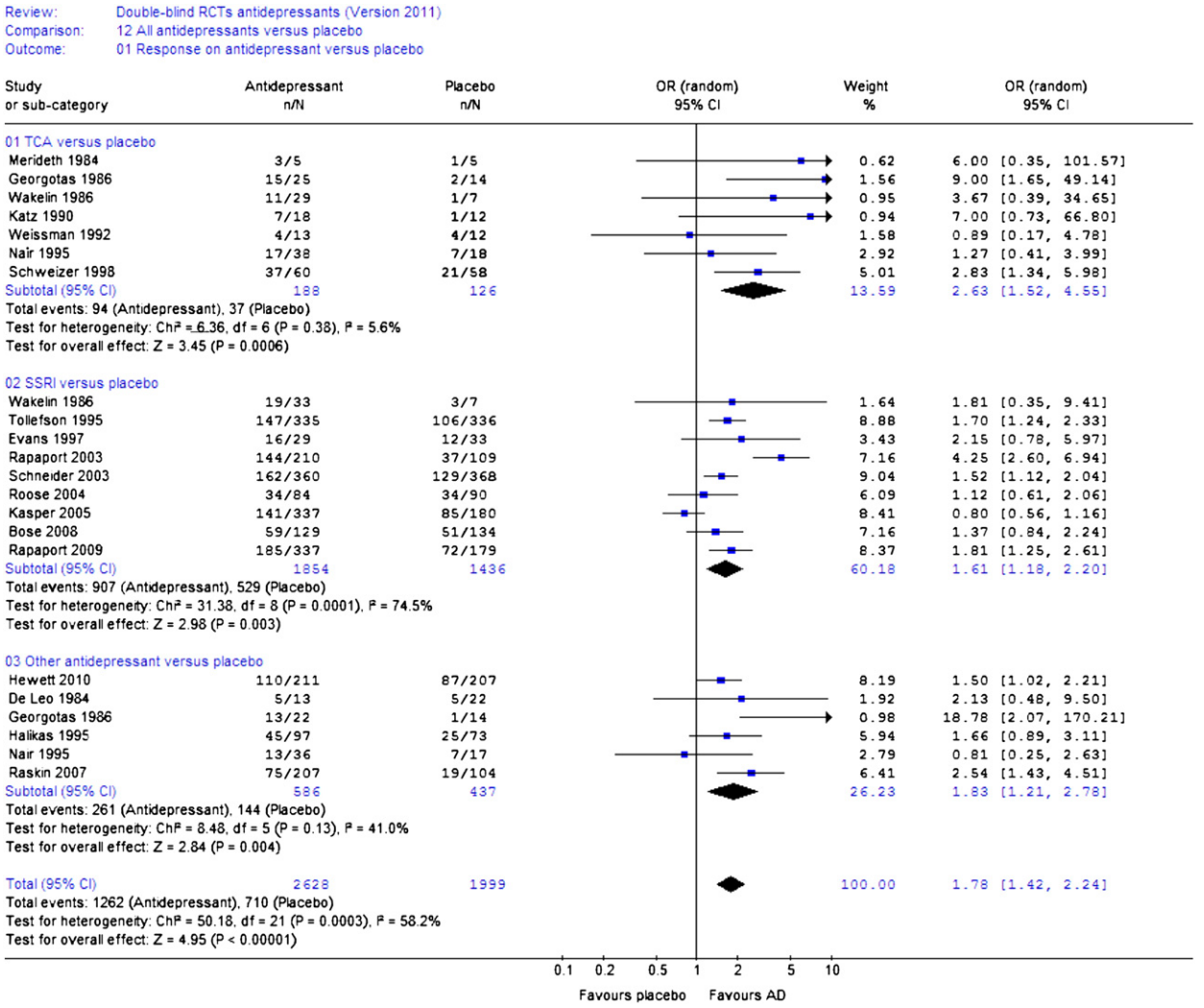

Fig. 3. Response on HAM-D, MADRS or CGI in TCAs, SSRIs and other antidepressants compared with placebo.

Gerner et al., 1980; Kok et al., 2007; Nair et al., 1995; Tignol et al., 1998; Trick et al., 2004; Waite et al., 1986), nor between SSRIs compared with other antidepressants (four RCTs; Falk et al., 1989; Karlsson et al., 2000; Schatzberg and Roose, 2006; Schatzberg et al., 2002) (Fig. 4). Two studies without extractable remission data found no difference between imipramine and reboxetine in patients with major depression (Katona et al., 1999) and between amitriptyline and citalopram (Rosenberg et al., 2007), respectively.

In the 27 RCTs that used our secondary outcome criterion response, no significant difference could be demonstrated between TCAs and SSRIs (11 studies with OR 0.85; 95% CI = 0.69–1.04) (Bondareff et al., 2000; Cohn et al., 1990; Feighner and Cohn, 1985; Forlenza et al., 2001; Geretsegger et al., 1995; Hutchinson et al., 1991; Kyle et al., 1998; Limosin et al., 2006; Rahman et al., 1991; Wakelin, 1986; Wehmeier et al., 2005), nor between TCAs and other antidepressants (7 studies with OR 1.29; 95% CI = 0.95–1.75) (Hoyberg et al., 1996; Kok et al., 2007; Mahapatra and Hackett, 1997; Nair et al., 1995; Schifano et al., 1990; Tignol et al., 1998; Trick et al., 2004), nor between SSRIs and other antidepressants (9 studies with OR 1.81; 95% CI = 0.85–3.89) (Allard et al., 2004; Bocksberger et al., 1993; Dalery and Aubin, 2001; Dorman, 1992; Guelfi et al., 1999; Karlsson et al., 2000; Oslin et al., 2003; Schatzberg et al., 2002; Weihs et al., 2000). Excluding both studies (Karlsson et al., 2000; Oslin et al., 2003) that included a small minority of patients with dementia and depression did not have a significant change on the results.

Again, funnel plots failed to demonstrate clear evidence of publication bias. Adding the results of one study we previously excluded because it had not been published (Giakis et al., 1993, results mentioned in Katona and Livingston, 2002) did not have a significant change in the OR.

All 19 RCTs that did not produce extractable response data found no differences between classes of antidepressants (Altamura et al., 1989a,1989b; Ather et al., 1985; Biziere and Berger, 1990; Bloeink et al., 1985; De Ronchi et al., 1998; De Vanna et al., 1990; Dunner et al., 1992; Eklund et al., 1985; Feighner et al., 1988; Katona et al., 1999; La Pia

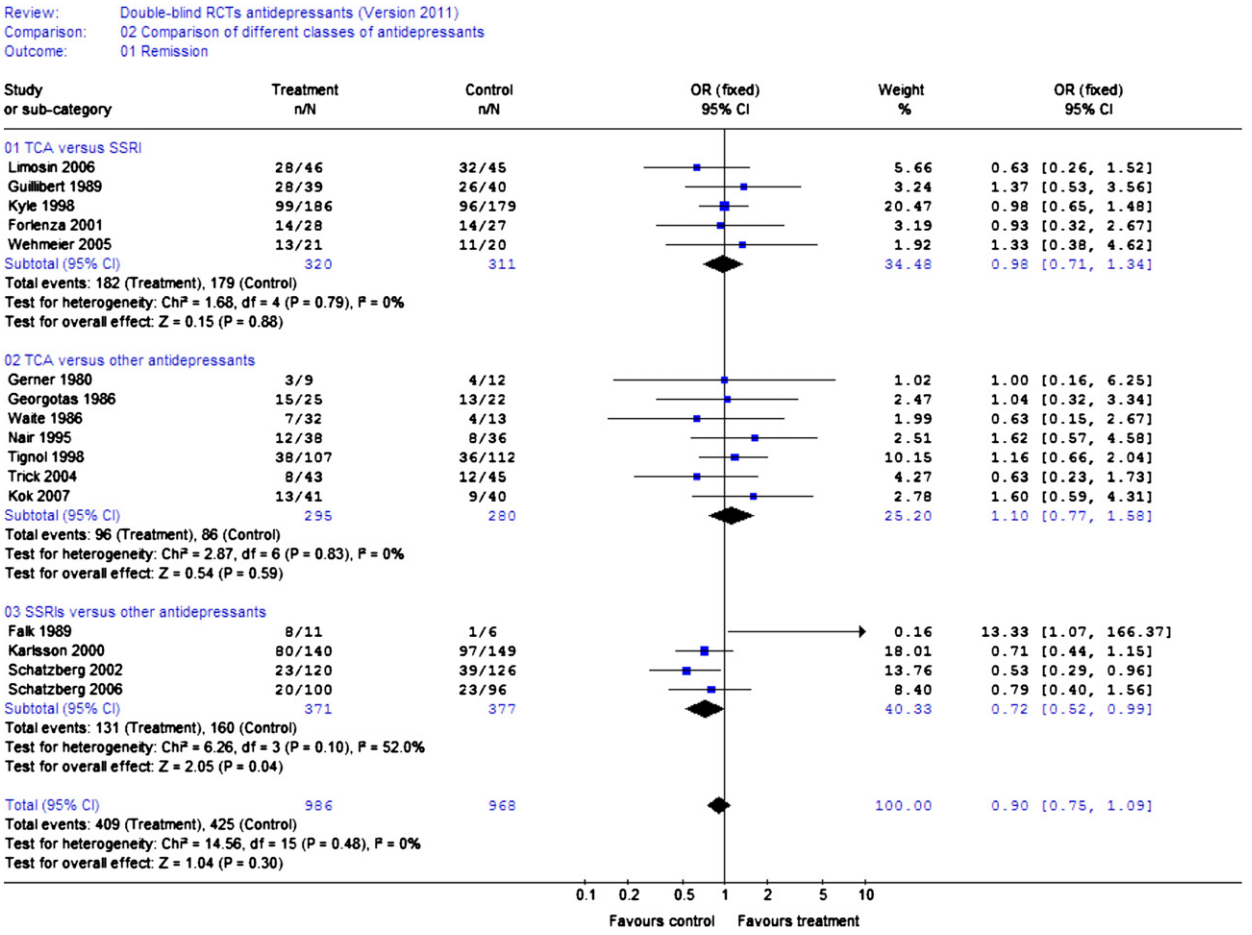

Fig. 4. Remission rates in head-to-head studies of TCAs, SSRIs and other antidepressants.

et al., 1992; Mulsant et al., 2001; Pancheri et al., 1994; Pelicier and Schaeffer, 1993; Phanjoo et al., 1991; Rosenberg et al., 2007; Siegfried and O'Connolly, 1986; Smeraldi et al., 1998).

3.3. Different efficacy between classes of antidepressant classes in subgroups of patients

Our next research question concerned possible differences in efficacy between classes of antidepressants among specific subgroups of older depressed patients. Our first subgroup was inpatients. Unfortunately, only 3 RCTs comparing different antidepressants and reporting remission data included only inpatients: in these studies no differences were found between TCAs and SSRIs or other antidepressants (Kok et al., 2007; Limosin et al., 2006; Waite et al., 1986). There were also no differences between classes of antidepressants in the five inpatient studies with response as outcome criterion (Bocksberger et al., 1993; Geretsegger et al., 1995; Kok et al., 2007; Limosin et al., 2006; Oslin et al., 2003) and in 5 studies with no extractable data to enter our meta-analysis (Altamura et al., 1989b; Bloeink et al., 1985; De Vanna et al., 1990; Eklund et al., 1985; Siegfried and O'Connolly, 1986).

The second subgroup was patients with a more severe depression. No difference could be demonstrated between TCAs and SSRIs in more severely depressed patients, neither in achieving remission (2 studies with OR 0.81; 95% CI = 0.40–1.65) (Limosin et al., 2006; Wehmeier et al., 2005) nor in achieving response (5 studies with OR 0.73; 95% CI = 0.50–1.07) (Cohn et al., 1990; Limosin et al., 2006; Rahman et al., 1991; Wakelin, 1986; Wehmeier et al., 2005).

It was not possible to perform subgroup meta-analyses of the trials among medical inpatients ($n = 2$) or nursing home patients ($n = 2$) without dementia, because these few studies also had too many differences in outcome criteria and antidepressant classes. Two of these 4 RCTs compared an antidepressant with placebo; in both RCTs no significant difference in favor of the antidepressant could be demonstrated. However, in both RCTs a type 2 error may explain the negative results as only a limited number of patients were included (Evans et al., 1997; Katz et al., 1990).

4. Discussion

Our systematic review included 92 double-blind RCTs in depressed older patients, of which 51 were pooled into one of the meta-analyses. Other reviews limited to double-blind RCTs have included only 10–18 RCTs (Katona and Livingston, 2002; Mittmann et al., 1997; Mukai and Tampi, 2009; Nelson et al., 2008; Sneed et al., 2008). The median

number of RCTs included in reviews using lesser strict criteria is only 18 (McCusker et al., 1998; Mottram et al., 2006; Pinquart et al., 2006; Rajji et al., 2008; Taylor and Doraiswamy, 2004; Williams et al., 2000a; Wilson et al., 2001). One important reason for the higher number of RCTs included in our meta-analyses is that we were able to find 13 publications that were identified as 'not published' in other reviews (Mottram et al., 2006; Wilson et al., 2001).

Our review also differs from other reviews in comparing the results of studies that entered our meta-analyses with studies that did not produce extractable data to enter the meta-analysis. This is important as the majority of RCTs are usually excluded in reviews, and because the choice of outcome criteria for entering the meta-analysis is somewhat arbitrary. For example, including only studies using ≥50% reduction on the MADRS or HAM-D as outcome criterion implies that studies using other percentages reduction on these depression scales and studies using only other scales are excluded. However, the results of studies that could not enter our meta-analysis were in line with the studies that could enter the meta-analysis.

Our results confirm the efficacy of antidepressants in older depressed patients when compared with placebo as found in previous reviews (McCusker et al., 1998; Mittmann et al., 1997; Nelson et al., 2008; Taylor and Doraiswamy, 2004; Williams et al., 2000a; Wilson et al., 2001). Remission is achieved by 33.7% of patients treated with antidepressants included in the meta-analyses (669 out of 1986 patients, Fig. 2) compared with 27.2% in patients using placebo (383 out of 1408 patients). Response is achieved by 48.0% of patients treated with antidepressants included in the meta-analyses (1262 out of 2628 patients, Fig. 3) compared with 38.6% in patients using a placebo (710 out of 1999 patients). Our remission and response rate were comparable with the 32.6% and 44.4% found for second generation antidepressants (SGA) in another meta-analysis, respectively (Nelson et al., 2008). Our study is the first meta-analysis using remission defined as a score below a predefined cut-off on a depression rating scale as primary outcome. The Cochrane review of Wilson also presented NNT for remission, but their definition of recovery or remission ('according to the trialists' own criteria') was less strict than our definition (Wilson et al., 2001). This may explain the lower NNT for remission, which varied between 3.2 and 8.5 in different antidepressant classes (Wilson et al., 2001). The NNT for response in our study (6.7; 95% CI 4.8–10) is comparable with the NNT for response of 8 (95% CI 5–11) in another review (Taylor and Doraiswamy, 2004).

Although pooling of all antidepressants together resulted in a statistically significant higher OR for remission compared with placebo, this was not the case if the 3 classes of antidepressants were analyzed as subgroups. Using response as outcome criterion, the differences between the 3 classes of antidepressants and placebo remained significant. This lack of separation from placebo in smaller subgroups may in part be explained by a type 2 error, as only 3 trials using TCA's and 4 trials using other antidepressants present remission data. The result of SSRIs versus placebo (7 trials) concerning remission would have been statistically significant, if we would also have used a fixed effect model (OR 1.31; 95% CI = 1.10–1.56), as was used by Wilson et al. (2001). However, the significant heterogeneity in our data implied that the random effect model should be used and this is a more conservative estimate. This may also in part explain the rather high NNT for remission in our study.

Another research question was whether there are differences in efficacy between the various classes of antidepressants. In the studies directly comparing different classes of antidepressants, the data to day do not indicate a difference in achieving remission or response, although some comparisons included only 4 or 5 RCTs. All previous reviews vary in classifying different types of antidepressants, but nevertheless also found no statistically significant differences in efficacy of TCAs versus SSRIs, MAOIs or atypical antidepressants regarding number of responders (Mittmann et al.,1997; Mukai et al., 2009; Williams et al., 2000a) or ORs for response (Wilson et al., 2001), although these reviews varied in the classification of antidepressants.

Even if all antidepressants would be equally effective in older patients as a group, this may not be the case in all patients. Our review is, to the best of our knowledge, the first in older patients that tried to replicate the findings in the meta-analysis of Anderson comparing TCA and SSRIs in different subgroups. When using the same method as Anderson to divide studies in those with less and more severe depressed patients, we also found no differences in efficacy of TCAs compared with SSRIs in studies with more severely depressed older patients. The approach Anderson used to identify studies with more severe depression, a median split on the HAM-D or MADRS, can be criticized for its lack of clinical utility. A more useful approach for clinicians would be to define severe depression as a minimum score on a depression rating scale. This approach is hampered by the use of different versions of the HAM-D (17, 21 and 24 items). Using a mean MADRS score of ≥30 as definition of severe depression did not produce a different outcome. Too few studies have included more severely depressed patients and therefore a replication of the important finding that antidepressants only separate from placebo in more severely ill patients, as suggested in a review of all trials submitted to the FDA for the licensing of 4 new generation antidepressants, was not possible (Kirsch et al., 2008). We were also not able to replicate Anderson's finding (Anderson, 2000) regarding a better efficacy of TCAs among inpatients, as there are not enough studies in older patients using the same outcome criteria to compare TCAs with SSRIs among only psychiatric inpatients.

Meta-analyses are only possible if studies use more homogeneous outcome criteria. Many of the RCTs we have identified however, did not use one of the established outcome criteria in depression research. Therefore, we strongly recommend that RCTs should always report their outcome both as response (≥50% decrease on HAM-D or MADRS, or CGI-I scores of 1–2) and as remission (final score below an internationally accepted cut-off on HAM-D or MADRS). Moreover, continuous outcomes such as the change in scores on rating scales should not only be presented in graphs but also in the exact value with a standard deviation, as the last are necessary for a meta-analysis.

5. Limitations

An important limitation is that we could only find 4 controlled trials that have not been published, although it was

not clear which of these studies were randomized and double-blind (Cassano et al., 1998; Giakis et al., 1993; Elly Lilly, 1993; Tourigny-Rivard et al., 1996). Two additional randomized studies were published with only an abstract available, and it is not stated if these studies were double-blind (Dong-Ming et al., 2006; Mingjun, 2007). If the results of the 2 studies of which the data are presented in other reviews were included in our analysis, the main results did not change (Giakis et al., 1993; Elly Lilly, 1993). In addition, our funnel plots did not demonstrate clear evidence of publication bias in older patients, which was also found in the most recent Cochrane review of antidepressants in the elderly (Mottram, et al., 2006).

A second limitation is that in some of our analyses, the I^2 statistic suggested considerable heterogeneity in our data questioning whether pooling of studies is allowed. We have applied the random effect model in case of substantial heterogeneity instead of the fixed effect model in these analyses. However, it is important to understand that this heterogeneity may come from multiple factors, as e.g. differences in setting, lower age limit, dose of antidepressant, comedication allowed, exclusion of patients with physical illnesses. Another limitation is that we did not weight the quality of the included studies. However, all studies used in the meta-analysis were randomized and double blind, used established criteria for diagnosing depression, used a standardized rating instrument to assess efficacy, and we presented only intention to treat (ITT) analyses. A more formal assessment of trial quality used in the most recent Cochrane review in the elderly found all included studies classified in the same quality group (Mottram et al., 2006) and we expect this would also be true in our meta-analysis.

A third limitation is that the group of other antidepressants is very heterogeneous, including antidepressants like venlafaxine, bupropion, moclobemide and trazodone. Although this was in line with other reviews and there is no agreement in the literature how to split up this heterogeneous group, this may lead to difficulties in interpreting the results of this group.

6. Summary

This extensive systematic review confirmed the efficacy of antidepressants. The results of the meta-analyses were in line with the majority of RCTs that did not produce extractable results to enter the meta-analysis. All classes of antidepressants were equally effective, also in more severely depressed older patients. As other reviews suggested that patients receiving SSRIs are less likely to be withdrawn due to side effects compared with TCAs, SSRIs may be the best treatment option in older depressed patients. These meta-analyses with 51 RCTs with an additional 41 RCTs not included in the meta-analyses, suggest that antidepressants are well studied for the acute phase treatment in older patients with unipolar major depression. However, there is a paucity of double-blind RCTs in treatment-resistant depression ($n=1$), psychotic depression ($n=1$), minor depression ($n=2$), and in depressed nursing home patients ($n=5$). Many reviews state that more research is needed, and we suggest that this should be primarily in the areas that are understudied.

Conflict of interest

Rob M. Kok has received a research grants from Wyeth and Lundbeck and has received speaker's honoraria from GlaxoSmithKline, Lundbeck, Pfizer and Wyeth.

Thea J. Heeren has received speaker's honoraria from Eli Lilly and Lundbeck.

Willem A. Nolen has received research grants from Astra Zeneca, GlaxoSmithKline and Wyeth; has served as consultant for Astra Zeneca, Eli Lilly, GlaxoSmithKline, Johnson & Johnson and Pfizer and has received speaker's honoraria from Astra Zeneca, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Organon and Pfizer.

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