**Predictors of treatment outcome in depression in later life: a systematic review and meta-analysis**

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**Introduction**

Depression in late-life is one of the most prevalent and disabling disorders for the elderly. Although, various pharmacologic and psychosocial treatments are available, a significant portion of patients with late-life depression remain symptomatic or have a delayed recovery ([Roose and Schatzberg, 2005](#_ENREF_124)). Differentiating those who are likely to have a good or poor response to treatment may have useful clinical applications: i) to inform patients about prognosis; ii) to speed up treatment adjustment; and iii) to tailor appropriate treatments to specific patients. A predictor is a variable or set of variables that can determine the possible outcome of an intervention in a population ([Nierenberg, 2003](#_ENREF_106)). Predictors can be identified from demographic data, clinical characteristics, and routine and specific investigation results.

There are only a limited number of reviews of predictors of treatment outcome in late-life depression. [Alexopoulos et al. (1989)](#_ENREF_9) reviewed the literature, and argued that the results of predictor studies which had used mixed-age populations might not be applicable to geriatric populations. They suggested that comorbid medical illness, duration of depressive episode, dysthymia and “double depression” (dysthymia in addition to major depression), personality disorder and neuroimaging abnormality predicted chronicity of a depressive episode in older adults. In a meta-analysis of RCTs of cognitive behavioural therapy, [Gould et al. (2012)](#_ENREF_50) found that treatment-related, study design and quality-related factors (such as concurrent pharmacotherapy, use of an active or non-active control, type of outcome measure and selective outcome reporting), but not demographic or clinical variables, were associated with the magnitude of treatment outcome. In a patient-level meta-analysis, [Nelson et al. (2013)](#_ENREF_104) reported three predictors that moderated drug- placebo differences from 10 RCTs of second-generation antidepressants in late-life depression; increased age, illness duration from first onset and depression severity. In their meta-regression of 34 RCTs of antidepressants in older people with major depression, [Calati et al. (2013)](#_ENREF_26) showed that male sex, increasing age, being Caucasian, less severe baseline depression and longer duration of episode had negative effects on the outcome of antidepressant treatment. [Pimontel et al. (2016)](#_ENREF_109) found in their meta-analysis that impairments in executive functioning, specifically planning and organisation, were associated with poorer immediate antidepressant treatment response. [Aizenstein et al. (2014)](#_ENREF_4) showed in their review that brain volume loss, lower white matter integrity and alteration of activity seen in fMRI in certain regions were associated with poorer treatment outcomes. Further, [De Crescenzo et al. (2016)](#_ENREF_34) found in their systematic review that FDG-PET imaging may predict treatment response to antidepressants by showing reduced glucose uptake in several brain areas.

To the authors' knowledge, no recent systematic review and meta-analysis has examined predictors of treatment outcome in a broad range of treatments for late-life depression (including pharmacological, psychological, psychosocial and care management interventions). A previous comprehensive review of treatments was conducted in 1989 and is clearly in need of updating given the number of studies that have been published since then ([Alexopoulos et al., 1989](#_ENREF_9)). The aim of this systematic review was to identify and critically appraise predictors of treatment outcome in RCTs of any intervention in comparison to active or non-active control conditions (e.g. placebo or treatment as usual) for late-life depressive disorder. The aim of the meta-analysis was to calculate the aggregated effect size of consistently reported predictors. Outcomes of interest included treatment response, remission or change in score on standardised depression questionnaires.

**Method**

*Identification of studies*

Online bibliographic databases (Pubmed, Embase, CINAHL, PsychINFO and Web of Science - all years) were searched on 6 December 2016. References of published reviews and studies were also manually searched. . The following terms were used to search the databases:

(depress\*) AND (“older adult” OR “old age” OR elder\* OR geriatr\* OR “late onset” OR late-onset OR “late life” OR late-life) AND (random\* OR RCT OR “clinical trial” OR “control\* trial\*”) AND (predict\* OR moderat\* OR mediat\* OR regress\*)

Titles and study abstracts were initially screened by CT in order to determine eligibility for retrieval. Retrieved articles were then screened for eligibility and selected for inclusion using a structured proforma. Studies were independently and blindly screened and selected by CT and co-authors (RLGa, HG, MC, EW, GR, TS or AT), and disagreements were resolved through discussion. Unresolved discrepancies were discussed with RLG.

*Inclusion/exclusion criteria*

Studies were included if they met the following criteria:

1. Peer-reviewed RCT or secondary analysis of data from a peer-reviewed RCT;
2. Any intervention (e.g. pharmacological, psychological, psychosocial or care management);
3. Non-active (e.g. treatment as usual) or active control condition (e.g. placebo), or other comparative treatment condition;
4. Sample size was greater than 5 in each condition;
5. Participants were aged 60 or more (studies including older and younger participants were included only if separate analyses were conducted for older participants);
6. Participants had diagnosis of major depression according to DSM/ICD criteria or established criteria;
7. Reported statistical significant data on predictors, moderators or mediators of treatment outcome, specifically, treatment response, remission and/or change in the score on standardised depression questionnaires;
8. In English language.

*Assessment of study quality*

The Quality Assessment Tool for quantitative studies from the Effective Public Health Practice Project (EPHPP) ([Thomas et al., 2004](#_ENREF_141)) was used to assess study quality. In addition, critical appraisal criteria were developed in order to assess the quality of predictor analyses (and hence findings), based on a systematic review by Knopp et al. ([Knopp et al., 2013](#_ENREF_65); [Pincus et al., 2011](#_ENREF_110); [Sun et al., 2012](#_ENREF_139)) . These criteria were:

1. Whether the predictors were assessed by a validated assessment tool as the validity and reliability of the assessment tools will ensure the accuracy of the predictors;
2. Whether the predictors were measured before randomisation or delivery of the intended intervention as some baseline factors may change after the allocation or be changed by the awareness of allocation;
3. The number of tested predictors was less than 5 as the fewer factors analysed, the greater reliability and credibility to accept or reject the predictors;
4. Whether there was a hypothesis in relation to the predictors as the selection of analysed factors should be based on theory or evidence in order to confirm meaningful predictors;
5. Whether there was an analysis of interactions between predictors and treatment arms as this may reveal underlying moderator effects.

Studies were independently and blindly rated by CT and co-authors (RLGa, HG, MC, EW, GR, TS or AT), and disagreements were resolved through discussion. Unresolved discrepancies were discussed with RLGo.

*Data extraction*

Data on a range of clinical and research characteristics were extracted using a structured proforma. Data were extracted independently and blindly by CT and co-authors (RLGa, HG, MC, EW, GR, TS or AT), and disagreements were resolved through discussion. Unresolved discrepancies were discussed with RLGo. Original studies were also retrieved and data extracted if studies of secondary data analyses provided insufficient information.

*Meta-Analysis*

Effect size

Predictors included in the meta-analysis were reported by at least 3 studies from the systematic review. For each study, odds ratios or information that could be used to calculate odds ratios were independently extracted by two authors (CT and KK). Any disagreements were resolved through discussion. Studies were excluded from the meta-analysis if insufficient data were reported to calculate odds ratio effect sizes. The effect size of interest was the overall effect size that included information from both treatment and comparison arms to reflect a difference in outcome for each predictor. Odds ratios were selected as the effect size of choice for this review for two reasons: i) it was the most frequently reported effect size in the included studies (18 out of 36 studies); and ii) conversion of odds ratios into other effect sizes tends to result in over- or under-estimation of effect sizes ([Lipsey and Wilson, 2001](#_ENREF_79)). Odds ratios were obtained through direct extraction from included studies, calculations from factorial tables or conversions from other reported effect sizes. Results from studies that only reported statistical outcomes were converted into standardised mean differences using an effect size calculator ([Wilson, 2001](#_ENREF_147)), and then converted to odds ratio using Hasselblad and Hedges’ method ([Hasselblad and Hedges, 1995](#_ENREF_52)). This has been shown to be the most robust method for this type of effect size conversion ([da Costa et al., 2012](#_ENREF_33)) .

Statistical analysis

Only predictors that were reported in 3 or more different studies were included in the meta-analysis. If studies reported more than one type of outcome measure for the same predictor, only one outcome was extracted. These were prioritised in the following order; remission, response (i.e. percentage reduction in score) and score or categorical outcome (e.g. high persistent, high decline and low decline). Remission was prioritised because it often reflects the use of more rigorous criteria and longer term improvement of symptoms than response, or changes in score or category of severity.

Separate meta-analyses were conducted for predictor variables that were reported in at least 3 different studies. Odds ratios were log-transformed for input into meta-analyses and back-transformed for reporting purposes. Random-effect models were used to aggregate the effect sizes ([DerSimonian and Laird, 1986](#_ENREF_35)). Statistical significance of the estimated overall odds ratio in each meta-analysis was examined using the Z test. Cochran’s Q-test of heterogeneity and *I2* statistic were calculated to examine between-study variability due to heterogeneity rather than sampling error or chance. Values of 0, 25, 50 and 75% indicated no, low, moderate and high heterogeneity respectively ([Higgins et al., 2003](#_ENREF_54)). Publication bias was estimated using Egger’s regression asymmetry test, which is suitable for small numbers of studies ([Egger et al., 1997](#_ENREF_39)). If publication bias was detected, a nonparametric trim-and-fill method was used to impute missing studies and re-estimate the pooled effect size ([Duval and Tweedie, 2000](#_ENREF_38)) . An alpha level of 0.05 was used for tests of the estimated overall odds ratio and publication bias, while 0.10 was used for tests of heterogeneity due to reductions in sensitivity of Cochran's Q test with small numbers of studies. Using the same procedures as above, subgroup analyses were performed in order to examine whether any between-study heterogeneity could be explained by type of treatment. Differences in overall effect sizes between subgroups were assessed using a test of heterogeneity. Bonferroni-corrections were applied to alpha levels in order to control for the risk of false positives across multiple subgroup analyses. Data were analysed using Stata 14.0 (StataCorp, College Station, TX).

**Results**

As shown in the PRISMA flow diagram (Figure 1), 6,706 articles were identified through database searches and 19 additional articles were identified from manual searches of related reviews. After removing duplicates, 4,869 articles were initially screened. The full-texts for 207 articles were retrieved and further screened for eligibility. 67 articles were selected after screening.

*Demographic and clinical characteristics*

Demographic and clinical characteristics were variable across studies, and some data could not be extracted for several studies (Table 1). About half of the studies included 100-500 participants, with 7 studies including more than 500 and 3 studies including more than 1000. The majority of studies included participants with a mean age greater than 70 (38/67), who were female and of white ethnicity. The Mini-Mental State Examination, a brief cognitive screening tool, was used to screen for dementia in most of the studies (49/67). Most of the included studies used the Hamilton Depression scale in recruitment and monitoring the participants (63/67), and the majority included participants with moderate to severe depression (25/67 with 15 not available).

*Study characteristics*

Eligible studies shared considerable similarities with respect to study characteristics (see Table 2). Studies were published from 1994 to 2016. Most of the studies used DSM-related diagnostic criteria, only 4 used other diagnostic systems. Treatment in the majority of studies comprised antidepressant medications (38/67); in addition, 19 studies involved a care management intervention and 15 studies investigated psychological treatments. Further, 37 studies utilised placebo or treatment-as-usual as control conditions; 30 studies used different antidepressants, biological or psychosocial interventions as comparator conditions. Most of the included studies involved secondary data analyses (45/67); only 22 examined predictors in their primary analyses. 40 studies had a duration of follow-up of 12 weeks or less, and only 12 studies monitored participants for at least 1 year.

*Quality assessment*

As shown in Table 3, the components of the quality assessment tool that were most adequately addressed were study design, data collection methods, confounders and selection bias. The least adequately addressed component was intervention integrity. All studies received a strong rating for study design as only RCTs were included in the review. 98.5%, 95.5%, 88.1% and 83.6% of studies had a moderate to strong rating for data collection methods, analysis, confounders and blinding, respectively. In contrast, 71.6% of studies had a moderate to strong rating for selection bias, and withdrawal and drop-outs. Furthermore, the majority of studies (68.7%) received a weak rating for intervention integrity, which involved assessing whether participants receiving the allocated intervention, measurement of intervention consistency and intervention contamination control.

Critical appraisal of the quality of predictor analyses showed that most studies generally reported satisfactory analyses (see Table A in the Appendix). 97.0% of studies used validated assessment tools to assess predictors. 76.1% had measured predictors before randomisation or receiving intervention. 56.7% had analysed less than 5 predictors and 70.2% had an a priori hypothesis in relation to the predictors. However, only 46.3% of studies tested for an interaction between predictors and treatment type.

*Predictors of treatment outcome*

Statistically significant predictors of treatment outcomes (with respect to treatment response, remission and/or change in depression scores) are reported in Table 3. Although 65 different statistically significant predictors were identified, only 7 were reported by at least 3 studies. These predictors were age, baseline depression severity, early improvement, current episode duration, baseline anxiety symptoms, physical illness and set shifting in the trail making test. Nine predictors were reported by two studies, and 49 predictors were reported by only one study.

The types of treatment that were examined in the studies that reported these 7 predictors are illustrated in Figure 2. The same type of relationship between treatment outcome and the predictor variable (i.e. positive or negative) was reported for all predictors, with the exception of age and baseline depression.

*Meta analyses*

Only five out of the seven above predictors were submitted to meta-analyses due to insufficient data to calculate effect sizes for two predictors (early improvement and current episode duration). Out of the five predictors submitted to meta-analyses, baseline anxiety, baseline depression and the trail making test were the only predictors that remained statistically significant after effect size aggregation (see Table 4). Physical illness showed a marginal significant effect in the meta-analysis. However, high levels of heterogeneity were found in all meta-analyses, with the exception of the trail making test. Furthermore, a statistically significant publication bias was found in the meta-analysis of baseline anxiety, baseline depression and physical illness. However, the pooled effect size remained unchanged after adjusting for publication bias using a trim-and-fill method.

*Subgroup analyses*

Predictor variables submitted to meta-analyses were additionally submitted to subgroup analyses organised by treatment type (biological vs. psychosocial vs. biological plus psychosocial). The biological sub-group consisted of pharmacological treatment and rTMS/ECT trials, the psychosocial group comprised psychological treatment trials, and the biological plus psychosocial group consisted of care management and combined treatment trials. After correcting for multiple comparisons, significant differences were found in subgroup analyses comparing type of treatment for age, baseline depression, baseline anxiety and physical illness, but not executive functioning (Table 5). Pooled effect sizes were mostly small to moderate in magnitude, with a considerable degree of within-group heterogeneity.

**Discussion**

Of the 65 statistically significant predictors identified from 67 studies of RCTs, only 7 were reported in at least 3 studies and only 5 of these provided sufficient information to permit a quantitative evaluation of effect sizes in meta-analyses. These will now be addressed in turn:

*Age*

Older age, as a predictor of treatment outcome, is controversial in our findings. Of the 6 studies reporting this variable, 4 reported a negative predictor relationship between age and outcome (the older the age, the poorer the outcome), while two studies reported a positive relationship. The study that reported a positive relationship showed a greater speed of response with older age but not overall response rate. Although, it would generally appear that older age is a negative predictor of good treatment outcome, which corresponds with previous meta-regression analyses ([Calati et al., 2013](#_ENREF_26)), our meta-analysis failed to show a statistically significant pooled effect size. A high level of heterogeneity may have been caused by variations in treatment modalities (e.g. pharmacotherapy, psychotherapy and care management) and outcome definitions. The subgroup analysis showed that older age had a small to moderate significant effect on the outcome, but only in biological treatment trials. Studies have suggested that age-related brain changes may lower the response to interventions through various mechanisms. For example, [Meltzer et al. (2001)](#_ENREF_86) demonstrated that serotonin-1A receptor density was decreased in healthy older adults compared with healthy younger adults, which may slow or reduce the effect of drugs targeting serotonin transmission. [Nahas et al. (2004)](#_ENREF_98) also reported that frontal lobe atrophy with advancing age reduced the effect of rTMS treatment. Further, [Ribeiz et al. (2013)](#_ENREF_119) found that reduced gray matter volume in the orbitofrontal cortex was associated with poorer antidepressant response in elderly patients, which suggests that treatment response may partly depend on the integrity of emotional regulation. In conclusion, older age may be a negative predictor of treatment outcome, especially in biological treatment trials, which can be explained by established age-related brain changes such as brain atrophy and serotonin receptor density reduction.

*Baseline depression severity*

Baseline depression severity was the most frequently reported statistically significant predictor in our systematic review, despite some inconsistencies among the studies. It was reported in 16 studies which used two different methods to identify predictors; the first involved examining overall treatment outcome, and the second focused on the effect of the intervention in order to delineate the drug-placebo difference.

When examining overall treatment outcome, 13 out of 16 studies reported a negative prediction relationship between baseline depression severity and treatment outcomes (the higher the baseline severity, the poorer the outcome). In addition, most of the studies reported this for remission. Several possibilities have been suggested to explain this association. First, [Ackerman et al. (1997)](#_ENREF_1) commented that it is easier to reach an endpoint if you start with a lower baseline score of depression. Second, [Nasser and Overholser (2005)](#_ENREF_101) observed that perceived social and emotional supports were associated with reduction of depression, and more severe depression might reduce access to these perceived supports, which may further diminish treatment response. Third, more permanent or severe underlying pathology may underlie more severe baseline depression, which may lessen the effect of treatment.

For analyses that focused on the drug-placebo difference, only 3 studies reported a positive direction for response and depression score, but not remission. Patients with a higher baseline depression severity demonstrated more of an antidepressant effect compared to placebo. This association has been suggested to be due to those with higher baseline severity having greater room for improvement than those with lower baseline severity ([Kirsch et al., 2008](#_ENREF_64); [Roose et al., 2004a](#_ENREF_122)).

A meta-analysis of 14 studies showed a small, but statistically significant overall effect size in negative direction for this predictor. However, high levels of heterogeneity were also found and therefore caution must be expressed when interpreting these results. The subgroup analysis showed that baseline depression was significantly associated with poorer outcome, but only in biological plus psychosocial treatment trials. However, the analysis also showed high levels of within-group heterogeneity. Our findings were different from other meta-analysis studies because we looked at the predictor’s effect on overall outcome, whereas others focused on the predictor’s effect on the differences between intervention and comparison groups. [Locher et al. (2015)](#_ENREF_80) did not find a relationship between baseline severity and change in symptoms in either antidepressant or placebo group in their meta-analysis. However, the study did not consider treatment duration in their analysis and limit to antidepressant studies, which may have produced the non-significant result. By contrast, two meta-analysis studies ([Khan et al., 2005](#_ENREF_62)) showed that more severe baseline depression was associated with a higher response rate to treatment, and therefore larger treatment effect in patients who had a longer illness duration. [Calati et al. (2013)](#_ENREF_26) suggested that a higher baseline depression group may have a better chance to reach the proportional reduction threshold than a lower baseline group. In conclusion, we found that higher baseline depression severity may be associated with poorer outcome in overall treatment. However, previous meta-analysis studies indicated that higher baseline depression may relate to more pronounced intervention effects than lower severity, though the reasons for this are unclear.

*Early improvement*

Early improvement was reported in 3 studies as a positive predictor of treatment outcomes. The range of what was considered as the early improvement period was from 1 week to 3 weeks. However, [Volz et al. (1995)](#_ENREF_146) suggested that the predictive value of early improvement on treatment outcome may be small. [Rodin and Voshart (1986)](#_ENREF_121) noted that an abrupt and transient improvement was associated with placebo response; however, gradual and persistence improvement was associated with antidepressant treatment. [Donovan et al. (1994)](#_ENREF_37) also observed that a significant portion of patients who did not respond to antidepressant in 4 weeks finally improved after 6 weeks of treatment which indicated low specificity of prediction. Thus, although early improvement was statistically identified as a predictor, its clinical value may be limited. It was not possible to submit this predictor to meta-analysis due to insufficient data.

*Current episode duration*

Current depressive episode duration was reported in 3 studies as a negative predictor; with longer episodes being associated with poorer outcome. This predictor has been reported in several studies, but the explanation was limited ([Alexopoulos et al., 1989](#_ENREF_9); [Calati et al., 2013](#_ENREF_26); [Goodkind et al., 2016](#_ENREF_49); [Moller et al., 2010](#_ENREF_88); [Pimontel et al., 2012](#_ENREF_108)). [Keller et al. (1986)](#_ENREF_61) suggested that episode duration was an intrinsic feature of each individual patient. As for baseline severity, a more permanent, chronic condition or severe underlying pathology may underlie a longer duration, which may lessen the effect of treatment and hence be associated with poorer response. Again, a meta-analysis was not conducted for this predictor due to insufficient data.

*Baseline anxiety symptoms*

Baseline anxiety symptoms were consistently reported in 7 studies as a negative predictor of treatment outcome. Furthermore, one additional study reported symptoms of worry and panic as a negative predictor too. A meta-analysis of 7 studies showed a statistically significant small to moderate negative overall effect size for this predictor. However, high levels of heterogeneity and statistically significant publication bias were also found and therefore caution must be expressed when interpreting these results. In the subgroup analysis, baseline anxiety was significantly associated with poorer outcome in biological treatment trials, but not biological plus psychosocial treatment trials. This finding is consistent with other reviews ([Goodkind et al., 2016](#_ENREF_49); [Moller et al., 2010](#_ENREF_88); [Pimontel et al., 2012](#_ENREF_108)). Although, [Nelson et al. (2009)](#_ENREF_103) reported that anxiety symptoms were not associated with the effect of antidepressant when compared to placebo, patients with comorbid anxiety symptoms had lower remission rates than the non-anxious group. Although overlapping genetic and neurobiological factors of depression and anxiety have been reported in previous studies ([Morimoto et al., 2012](#_ENREF_91); [Morimoto et al., 2011](#_ENREF_92)), more recent brain imaging studies have showed more distinct features between depression alone and depression with anxiety symptoms. For example, [Canu et al. (2015)](#_ENREF_27) revealed that patients with depression and anxiety may have more severe cortical atrophy in areas that correspond with anxiety symptoms than patients with depression alone. [Potvin et al. (2015)](#_ENREF_111) suggested that anxiety may be associated with smaller cortical thickness in the elderly. Furthermore, [Domschke et al. (2010)](#_ENREF_36) found that the neuropeptide Y gene, which was found in anxious depressed patients, affected antidepressant treatment response, and [Baffa et al. (2010)](#_ENREF_15) observed that serotonin gene variation influenced antidepressant treatment response in this group of patients. Based on these distinct clinical pictures and biological evidence, [Ionescu et al. (2013)](#_ENREF_56) suggested a differentiation between anxious depression and non-anxious depression. Late-life depression patients with anxiety symptoms may have more severe brain pathology or genetic vulnerabilities that reduce the effect of treatment. Co-morbid anxiety symptoms were associated with poorer outcome and may be an important sign that the patient needs additional treatment or will have a longer time to remission.

*Physical illness*

Physical illness (e.g. overall comorbidity diseases and chronic illnesses such as hypertension, diabetes, cancer and renal disease) were consistently reported as a negative predictor in 6 studies. In addition, 5 studies reported pain, cerebrovascular disease, limitation of physical function and dyspnoea-related disability to be negative predictors of treatment outcomes. By contrast, one study reported that headache before receiving treatment was related to better treatment response. A meta-analysis showed a very small and marginal statistically significant pooled effect size, in conjunction with a high level of heterogeneity. Although the subgroup analyses showed a significant difference between treatment types, this result should be interpreted with caution given that 4 out of 5 studies were biological plus psychosocial treatment trials. Physical illness may complicate depressive outcome through both biological and psychological pathways. Illnesses that directly affect the brain may interrupt neurotransmitter and neural network pathways, and non-neurological illness may indirectly affect the brain via inflammatory process and HPA axis regulation ([Brown et al., 2004](#_ENREF_24); [Marson et al., 1997](#_ENREF_83)). Furthermore, illnesses that result in disability and pain may induce additional psychological stressors such as lowered self-esteem, dependency, prolonged discomfort and loss of social relationships ([Rackley and Bostwick, 2012](#_ENREF_112); [Rodin and Voshart, 1986](#_ENREF_121)). In addition, depression may affect the course and incident of medical illnesses such as cardiovascular diseases, neurological diseases, diabetes and HIV ([Marson et al., 1997](#_ENREF_83)). Thus, physical illness may be a predictor of treatment outcome that not only influences depression prognosis but also is affected by depression.

*Executive functioning*

Performance on the Trail Making Test, particularly the ability to perform the set shifting task, was consistently shown to positively predict depression outcomes in 3 recent studies. In addition, the meta-analysis showed a moderate statistically significant effect size, with no evidence of heterogeneity or publication bias. No significant difference was found between treatment types in subgroup analyses for this predictor. However, this finding was contradicted in a recent cohort study in which the Trail Making Test was not associated with likelihood of remission ([Clery-Melin and Gorwood, 2017](#_ENREF_31)). This contradiction may be explained by the fact that the cohort study was done in adult population and low number of participants who completed the predictor assessment (25%). In addition, performance on other executive functioning tests might predict treatment outcome. Two studies showed that impairment in response inhibition in the Stroop test was related to worse outcome, and another study reported that higher scores on a coding task and processing speed were related to better outcome. This result is not supported by a recent meta-analysis which showed that only performance on planning and organisation tasks was related to treatment response ([Pimontel et al., 2016](#_ENREF_109)). However, this meta-analysis only included studies of acute (6- 12 weeks, mean 9.75 weeks) treatment outcome of antidepressants, whereas the current review included studies with much longer treatment durations (8-96 weeks, mean 26.00 weeks ) in various treatment conditions. Another meta-analysis review showed that only the Initiation-Perseveration subscale of the Mattis Dementia Rating scale, a verbal fluency test, was associated with antidepressant response ([McLennan and Mathias, 2010](#_ENREF_85)). A cohort study showed that Wisconsin Card Sorting Test, but not verbal fluency or Stroop test, was associated with response to cognitive behavioural treatment ([Goodkind et al., 2016](#_ENREF_49)). These inconsistencies in evidence in older patients may lead to the explanation that different executive function tasks specifically predict different treatment conditions.

Changes in frontal brain regions and neural networks may underlie the relationship between executive functioning and treatment outcome in late-life depression. For example, Alexopoulos et al. observed that patients with late-life depression who had impairment in executive functioning had poorer depression outcome ([Alexopoulos et al., 2005b](#_ENREF_6); [Alexopoulos et al., 2002](#_ENREF_7)). Furthermore, the impairment was linked to lower frontal subcortical and limbic volume. [Patel et al. (2015)](#_ENREF_107) reported that patients with late-life depression who had lower functional connectivity in the dorsal default mode network had better treatment outcome. [Karim et al. (2016)](#_ENREF_59) reported differences in brain activity in frontal and temporal cortices involving the anterior salience network and default mode network between remitted and non-remitted late-life depression patients. Therefore, intact executive function may indicate less severe pathology or preserved ability to respond to treatment.

*Clinical and research implications*

Predicting treatment outcome in late-life depression may aid clinicians in three ways: i) it may serve as a useful guide to seek out information that can be used to inform and influence clinical decisions; ii) it may aid better decision making (e.g. whether to switch or augment treatment); and iii) it may better inform patients about the possible prognosis. Identifying patients with good and poor outcomes with these predictors may lead to better understanding of the nature of late-life depression and new treatment options. However, current data on each predictor is still scarce. Further evidence of the validity and effect of these predictors is required, in addition to replications of these data. Further investigation of how predictors may be integrated into clinical practice to aid decision making is essential for the development of new treatments that could improve effectiveness for patients with poorer outcomes.

*Strengths and limitations*

The main advantage of this systematic review is the broad range of interventions for late-life depression that were considered, thus providing a comprehensive summation of the literature. The benefit of using data from RCTs is the low rate of data attrition that can cause observational bias in other types of studies.

However, there were a few limitations in this systematic review. Studies that were included were limited to data from peer-reviewed RCTs, rather than from grey literature such as clinical trials databases. Thus, this review may be subject to publication bias. A wider search including grey literature may have identified additional relevant studies to include in the review, although this may have introduced further bias as unpublished studies may be of lower methodological quality ([Egger et al., 2003](#_ENREF_40)). Furthermore, 67% of included studies were secondary analyses, which questions the statistical validity of the predictors that we have identified. For example, secondary analyses may have failed to detect statistically significant predictor variables simply due to being underpowered for these analyses. The analysis methods employed by different studies also varied, and so caution should be applied when interpreting the validity of the predictors as a group. However, the fact that the majority of studies used regression analysis may lessen this concern.

There were also a few limitations in the meta-analysis. A selection bias may have been introduced as studies were only included if they reported statistically significant predictors. Furthermore, small number of studies reported for each predictor variable, coupled with a variety of treatment modalities introduced high levels of heterogeneity. Therefore, although the results of the meta-analyses may be of clinical value, they should be interpreted with caution. Subgroup analyses examined whether any between-study heterogeneity in effect sizes could be explained by the type of treatment. However, these analyses were limited by small numbers of studies and considerable heterogeneity within at least one subgroup for each predictor. Furthermore, although significant subgroup differences were found for these predictors, the possibility that a moderating variable other than treatment type may have been responsible for these differences cannot be ruled out.

**Conclusions**

In this systematic review, we found that older age, higher baseline depression severity, slower improvement, longer current episode duration, higher co-morbid baseline anxiety symptoms, the presence of physical illness and impairment of executive functioning are predictors of poor treatment outcomes. Of these seven predictor variables identified in 3 or more studies, meta-analyses confirmed that baseline depression, baseline anxiety, physical illness and executive function and were significantly associated with treatment outcome. Subgroup analyses found differences in predictor effect between biological treatment trials, psychosocial treatment trials and biological plus psychosocial treatment trials. Other statistically significant predictors were identified from eligible studies, but there were very few replications of these predictors. These results come from post-hoc analyses of RCT data which may question the validity of these conclusions.

**Figure 1: PRISMA Flow Diagram**

Full-text articles excluded,
with reasons
(n = 140)

- no predictor analysed (33)

- subjects not old age (27)

- Other outcome(14)

- no full text available (abstract/poster) (14)

- not from RCT (13)

-no significant predictor reported (12)

- not in MDD (9)

-protocol (7)

- duplicate (6)

-review article (3)

-not in English(2)

Records identified through database searching
(n = 6,706)

Pubmed 1,155

Embase 1,960

Psychinfo 694

CINAHL 806

WoS 2,091

Studies included in qualitative synthesis
(n = 67)

Full-text articles assessed for eligibility
(n = 207)

Records excluded
(n = 4,662)

Records screened
(n = 4,869)

Records after duplicates removed
(n = 4,869)

Additional records identified through other sources
(n = 19)

## Screening

## Included

## Eligibility

## Identification

Studies included in
meta-analysis
(n = 32)

*Adapted from:*  [Moher et al. (2009)](#_ENREF_87)

**Figure 2: Bar chart of predictors reported in 3 or more studies, stratified by treatment type.**

**Figure 3: Forest plot of each predictors included in the meta-analysis**



**Table 1: Demographic and clinical characteristics**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study year country** | **Old age sample size** | **Mean age** | **Mean years of education** | **% women** | **% white ethnicity** | **Screening tool and mean cognitive score** | **Depression Rating scale name** | **Depression Rating scale criteria for ENTRY** | **Mean depressive severity at ENTRY** | **Mean age of onset** | **duration of illness at enter (wk)** |
| Ackerman 1997 US | 671 | N/A | N/A | N/A | N/A | MMSE (N/A) | HAMD17 | 16 | N/A | N/A | N/A |
| Ackerman 2000 US | 671 | N/A | N/A | N/A | N/A | MMSE (N/A) | HAMD17 | 16 | N/A | N/A | N/A |
| Adeoye 2000 US | 15 | 69.2 | N/A | 53.33 | 93.33 | N/A | HAMD | 15 | 19.06 | N/A | N/A |
| Alexopoulos 2005 US | 215 | N/A | 12.79 | 71.57 | 67.55 | MMSE (27.35) | HAMD | 18 | 18.8 | N/A | N/A |
| Alexopoulos 2014 US | 138 | 70.95 | 13.37 | 65.94 | N/A | MMSE (27.4) | HAMD17 | 14 | 19.05 | N/A | N/A |
| Alpert 2003 US | 22 | 67.28 | N/A | N/A | N/A | N/A | HAMD24 | 18 | 24.3 | N/A | N/A |
| Andreescu 2007 US | 170 | 76.68 | 12.95 | 64.75 | 92.04 | MMSE (N/A) | HAMD17 | 15 | 20.64 | 61.94 | 109.38 |
| Andreescu 2009 US | 166 | 76.63 | 13.03 | 65.06 | 92.77 | MMSE (N/A) | HAMD17 | 15 | core item subscale 7.08 | 61.85 | 109.63 |
| Azar 2011 US | 792 | 73.63 | \* | 32.45 | 37.25 | N/A | CES-D | N/A | 28.31 | N/A | N/A |
| Banerjee 1996 UK | 69 | 80.71 | N/A | 82.61 | N/A | N/A | MADRS | N/A | 26.25 | N/A | N/A |
| Bao 2011 US | 396 | \* | \* | 70.89 | 65.17 | MMSE (N/A) | CES-D | 20 | 20.54 | N/A | N/A |
| Beaudreau 2015 US | 46 | 70.78 | 15.78 | 65.2 | 69.6 | MMSE (N/A) | HAMD | 20 | 22.54 | N/A | N/A |
| Bjolseth 2015 Norway | 73 | 74.81 | N/A | 53.42 | N/A | MMSE (27.59) | HAMD17 | 18 | 24.72 | N/A | 28.4 |
| Bogner 2007 US | 599 | 70.3 | 12.8 | 71.6 | 70.2 | MMSE (27.4) | HAMD24 | N/A | 17.28 | N/A | N/A |
| Bogner 2012 US | 599 | 70.2 | 12.8 | 72% | 70.2 | MMSE (27.4) | HAMD24 | 10 | N/A | N/A | N/A |
| Bondareff 2000 US | 210 | 67.85 | \* | 59.04 | 93.81 | MMSE (N/A) | HAMD24 | 18 | 24.75 | 48.65 | 156† |
| Cappeliez 2007 Canada | 68 | N/A | \* | 67 | N/A | Physician's clinical judgment (N/A) | SCL-20 | N/A | 1.675 | N/A | N/A |
| Chan 2013 Singapore | 26 | 69.7 | \* | 80.8 | 0 | N/A | GDS-15 | 4 | 7.16 | N/A | N/A |
| Chan 2014 Singapore | 29 | \* | \* | 79.3 | 0 | N/A | GDS-15 | 4 | 5.47 | N/A | N/A |
| Coon 2003 US | 58 | 66.6 | 14.6 | 68.25 | N/A | MMSE (N/A) | HAMD | 15 | N/A | N/A | N/A |
| Evans 1997b  UK | 82 | 80.4 | N/A | 75.61 | N/A | MMSE (\*) | HAMD17 | N/A | 20.75 | N/A | N/A |
| Eyre 2016 US | 35 | 69.18 | 15.12 | 56.94 | N/A | MMSE (28.39) | HAMD24 | 16 | 18.86 | 40.17 | N/A |
| Fields 2012 US | 449 | 75.1 | \* | 46.5 | 94.2 | 3-MS (94) | GDS | 6 | 8.7 | N/A | N/A |
| Gasto 2003  Spain | 68 | 70.83 | N/A | 63.24 | N/A | MMSE (N/A) | HAMD17 | 21 | 26.52 | N/A | N/A |
| Ghesquiere 2014 US | 417 | 70.02 | 12.86 | 71.46 | 70.05 | MMSE (N/A) | CES-D | 20 | 17.95 | N/A | 202.24† |
| Gildengers 2002 US | 323 | 70.3 | 12.3 | 72.8 | 91.3 | MMSE (28.1) | HAMD17 | 15 | 22.1 | N/A | 22 |
| Gilman 2013  US | 1226 | \* | \* | 70 | 69.5 | MMSE (N/A) | CES-D | 20 | 11.4 | N/A | N/A |
| Greenlee 2010 US | 124 | 72.29 | N/A | 68.35 | N/A | MMSE (N/A) | HAMD17 | 15 | 18.48 | N/A | 131 |
| Heun 2013 multi centres | 222 | 71.84 | N/A | 68.96 | N/A | MMSE (29.17) | HAMD17 | 22 | 26.77 | N/A | 22.84 |
| Hsu 2016 US + Canada | 168 | 66 | 14 | 57 | 88 | MMSE (N/A) | MADRS | 15 | 28 | 40 | 104 |
| Jorge 2008 US | 92 | 63.67 | 13.89 | 55.43 | N/A | MMSE (28.1) | HAMD 17 | N/A | 18.57 | N/A | N/A |
| Kaneriya 2016  US + Canada | 181 | 67.36 | 14.16 | 56.91 | 87.87 | MMSE (N/A) | MADRS | 15 | 23.26 | N/A | N/A |
| Katon 2010 US | 871 | 71 | N/A | 63.83 | 78.64 | Six item cognitive screener (N/A) | SCL-20 | N/A | N/A | N/A | N/A |
| Kin 1997 multi centres | 95 | 69.68 | N/A | 70.34 | N/A | MMSE (28.68) | HAMD17 | 18 | 23.5 | N/A | N/A |
| Kok 2009a Netherlands | 82 | 72.24 | N/A | 72.84 | N/A | MMSE (25.93) | MADRS | 20 | 32.83 | N/A | 22.04† |
| Kok 2009b Netherlands | 81 | 72.21 | N/A | 72.84 | N/A | MMSE (25.89) | MADRS | 20 | 32.9 | N/A | 21.76† |
| Koran 1995 US | 671 | 68.6 | N/A | 55 | 94 | MMSE (29) | HAMD 21 | 16 | N/A | N/A | N/A |
| Korte 2012 Netherlands | 202 | 63 | \* | 76.7 | N/A | N/A | CES-D | 10 | 20.5 | N/A | N/A |
| Krahn 2006 US | 1531 | 73.9 | \* | 30.7 | 45.1 | Short form health inventory (37.6) | CES-D | N/A | 24.95 | N/A | N/A |
| Krishnan 2001 US | 220 | 67.99 | N/A | 61.83 | N/A | MMSE (28.54) | HAMD 24 | 18 | 24.86 | N/A | N/A |
| Laidlaw 2008 UK | 40 | 74 | 10 | 72.5 | N/A | MMSE (28.125) | HAMD24 | 24 | 11.6 | N/A | N/A |
| Mavandadi 2007 US | 524 | 73.77 | N/A | N/A | N/A | N/A | CES-D | N/A | 23.69 | N/A | N/A |
| Morse 2005 US | 160 | 67.7 | \* | 75 | 92.5 | MMSE (29.3) | HAMD | 17 | 22.5 | 47.9 | N/A |
| Mulsant 2001US | 116 | 72.1 | N/A | 71.6 | 86.2 | MMSE (56.5) | HAMD17 | 15 | 22.4 | 60.6 | 26 |
| Murphy 2013US | 246 | 71.85 | N/A | 51.62 | N/A | MMSE (28.7) | HAMD17 | 18 | 22.3 | N/A | \* |
| Narushima 2010 US | 43 | 62.85 | 14.07 | 58.05 | 97.66 | MMSE (27.82) | HAMD17 | 14 | 16.59 | N/A | N/A |
| Navarro 2001 Spain | 58 | 70.69 | N/A | 63.8 | N/A | MMSE (26.64) | HAMD | 21 | 26.76 | 66.07 | 6.71 |
| Rapaport 2003 US | 319 | 69.96 | N/A | 56.11 | 95.29 | MMSE (N/A) | HAMD17 | 18 | 22.17 | N/A | 180.96† |
| Raskin 2008 Canada | 311 | 72.83 | N/A | 59.48 | 78.14 | MMSE (22.86) | HAMD17 | 18 | 18.83 | N/A | 55.67 |
| Riebe 2012 US | 906 | 71 | \* | 56.1 | 78.3 | Six item cognitive screener (N/A) | SCL-20 | N/A | \* | N/A | N/A |
| Roose 2004 US | 174 | 79.6 | 13.8 | 58.1 | N/A | MMSE (28) | HAMD24 | 20 | 24.3 | 68.3 | 12.82 |
| Rosenthal 2005 US | 34 | 66 | N/A | N/A | 85 | MMSE (N/A) | BDI | N/A | N/A | 36 | N/A |
| Salloway 2002 US | 170 | 75.88 | N/A | sertraline 41%, citalopram 61% | 85 | MMSE (N/A) | HAMD17 | 18 | 23.09 | 62.77 | N/A |
| Sarginson 2010a US | 246 | 74.2 | N/A | 51.22 | 91.87 | MMSE (N/A) | HAMD17 | 18 | 22.35 | N/A | N/A |
| Sarginson 2010b US | 246 | 74.2 | N/A | 51.22 | 91.87 | MMSE (N/A) | HAMD17 | 18 | 22.33 | N/A | N/A |
| Schweizer 1998 US | 177 | 72 | N/A | 53 | N/A | N/A | HAMD 17 | 18 | 24.03 | 60 | \* |
| Singh 1997 US | 32 | 70.94 | 14.37 | 62.5 | N/A | MMSE (28.5) | BDI | 12 | 19.94 | N/A | 118.4† |
| Smagula 2016 US | 181 | 66 | 14 | 57 | 88 | N/A | MADRS | 15 | 28 | 40 | 104 |
| Small 1995 US | 671 | N/A | N/A | N/A | N/A | MMSE (N/A) | HAMD17 | 16 | N/A | N/A | N/A |
| Sneed 2007 US | 174 | 79 | \* | 58 | N/A | MMSE (N/A) | HAMD24 | 20 | 24 | 68 | N/A |
| Sneed 2008 US | 84 | 79 | N/A | 54 | N/A | MMSE (28.42) | HAMD24 | N/A | 24.4 | N/A | N/A |
| Sneed 2011 US | 38 | 66 | 15.7 | 63 | N/A | MMSE (27.5) | HAMD24 | 16 | 24.32 | 46.5 | N/A |
| Steffens 2006(Steffens et al., 2006) US | 1684 | 70.9 | N/A | 66.3 | 76.7 | Six item cognitive screener (5.55) | SCL-20 | N/A | 1.68 | N/A | N/A |
| Tan 1994 UK | 63 | 80 | N/A | 66.33 | N/A | AMT (N/A) | GDS | 15 | 16.8 | N/A | N/A |
| van Schaik 2006 Netherlands | 143 | 67.93 | \* | 69.48 | N/A | MMSE (26.35) | MADRS | N/A | 19.35 | \* | N/A |
| Volz 1995 Germany | 189 | 68 | N/A | 75.13 | N/A | N/A | HAMD | N/A | 26.2 | N/A | N/A |
| Zanetidou 2016 Italy | 121 | 75.14 | \* | 71.11 | N/A | MMSE (26.87) | HAMD17 | 18 | 20.14 | N/A | N/A |

*Note:* N/A = not applicable or not available, \* = data in categorical form, † = data calculated from months or years to weeks by multiply by 4 and 52, respectively.

*Cognitive screening tools* MMSE = Mini-Mental State Examination, AMT = Abbreviated Mental Test Score, 3-MS = The Modified Mini-Mental State

*Depression scales* HAMD = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Scale, CES-D = Center for Epidemiologic Studies Depression Scale , GDS = Geriatric Depression Scale, BDI = Beck Depression Inventory, SCL-20 = Hopkins Symptom Checklist

**Table 2: Study characteristics**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study year** | **Outcome** | **Setting** | **Diagnostic criteria used for MDD** | **Treatment condition(s)** | **Comparator / control condition(s)** | **Type of statistical analysis used for predictors** | **Study duration (in weeks)** | **Source RCT** |
| Ackerman 1997 | RES/REM | practice | DSM III | Fluoxetine | Placebo | Regression | 6 | [Tollefson et al. (1995)](#_ENREF_143) |
| Ackerman 2000 | RES/REM | practice | DSM III R | Fluoxetine | Placebo | Regression | 6 | [Tollefson et al. (1995)](#_ENREF_143) |
| Adeoye 2000 | RES | practice | DSM III R | Bupropion 150mg | Bupropion 75 mg | Bivariate | 3-11 | Primary |
| Alexopoulos 2005 | REM | practice | DSM IV | Care management | Usual care | Regression | 72† | [Bruce et al. (2004)](#_ENREF_25) |
| Alexopoulos 2014 | SCORE | practice | DSM IV | Personalised Intervention for depression and COPD | Usual care | Regression | 52† | Primary |
| Alpert 2003 | SCORE | mixed | DSM III R | Sertraline | Nortriptyline | Regression | 12 | [Bondareff et al. (2000)](#_ENREF_23) |
| Andreescu 2007 | RES | practice | DSM IV | Pharmacotherapy + Clinical management / Placebo + Clinical management / Pharmacotherapy + IPT / Placebo + IPT | Placebo | Survival analysis | 120 | [Reynolds et al. (2006)](#_ENREF_117) |
| Andreescu 2009 | RES | practice | DSM IV | Pharmacotherapy + Clinical management / Placebo + Clinical management / Pharmacotherapy + IPT / Placebo + IPT | Placebo | Bivariate | 104† | [Reynolds et al. (2006)](#_ENREF_117) |
| Azar 2011 | REM | practice | DSM IV | Integrated care model | Enhance specialty referral model | Regression | 24† | [Krahn et al. (2006a)](#_ENREF_72) |
| Banerjee 1996 | SCORE | practice | AGECAT | Psychogeriatric team | Usual care | Regression | 24† | Primary |
| Bao 2011 | SCORE | practice | DSM IV | Care management | Usual care | Regression | 96† | [Bruce et al. (2004)](#_ENREF_25) |
| Beaudreau 2015 | RES/REM | practice | DSM IV | Problem solving therapy | Supportive therapy | ROC analysis | 12 | [Arean et al. (2010)](#_ENREF_13) |
| Bjolseth 2015 | REM | practice | DSM IV TR | ECT bifrontal  | ECT right unilateral | Regression | 12 | Primary |
| Bogner 2007 | RES/REM | practice | DSM IV | Care management | Usual care | Regression | 16 | [Bruce et al. (2004)](#_ENREF_25) |
| Bogner 2012 | CAT | practice | DSM IV | Care management | Usual care | Regression | 96† | [Bruce et al. (2004)](#_ENREF_25) |
| Bondareff 2000 | SCORE | community | DSM III R | Sertraline | Nortriptyline | Survival analysis | 12 | Primary |
| Cappeliez 2007 | REM | practice | DSM IV | 8 weeks treatment plan + problem solving intervention (optional) | Usual care | Bivariate | 8 | Primary |
| Chan 2013 | SCORE | community | N/A | Life story book creation | Visit | Regression | 8 | Primary |
| Chan 2014 | SCORE | community | N/A | Life story review | Visit | Regression | 8 | Primary |
| Coon 2003 | SCORE | practice | RDC | CBT + Desipramine | CBT alone | Regression | 16† | [Thompson et al. (2001)](#_ENREF_142) |
| Evans 1997 | RES | practice | GMS/ AGECAT | Fluoxetine | Placebo | Regression | 8 | [Evans et al. (1997a)](#_ENREF_41) |
| Eyre 2016 | REM | practice | DSM IV | Methylphenidate + Citalopram | Methylphenidate / Citalopram | Bivariate | 16 | [Lavretsky et al. (2015)](#_ENREF_76) |
| Fields 2012 | SCORE | practice | not specified | Celecoxib/ Naproxen sodium | Placebo | Regression | 260† | [Lyketsos et al. (2007)](#_ENREF_81) |
| Gasto 2003 | REM | practice | DSM IV | Venlafaxine | Nortriptyline | Bivariate | 24 | Primary |
| Ghesquiere 2014 | REM | practice | DSM IV | Care management | Usual care | Regression | 16† | [Bruce et al. (2004)](#_ENREF_25) |
| Gildengers 2002 | RES | practice | DSM IV | Paroxetine | Nortriptyline | Regression | 12 | [Reynolds et al. (1999)](#_ENREF_118) |
| Gilman 2013 | SCORE | practice | DSM IV | Care management | Usual care | Regression | 104† | [Bruce et al. (2004)](#_ENREF_25) |
| Greenlee 2010 | REM | practice | DSM IV | IPT + Care management | Care management | Survival analysis | 16 | [Reynolds et al. (2010)](#_ENREF_116) |
| Heun 2013 | RES | practice | DSM IV TR | Agomelatine | Placebo | Regression | 8 | Primary |
| Hsu 2016 | REM | practice | DSM IV | Venlafaxine + Aripiprazole | Venlafaxine | Bivariate | 12 | [Lenze et al. (2015)](#_ENREF_77) |
| Jorge 2008 | SCORE | practice | DSM IV | rTMS | Sham | Regression | 1.5† | Primary |
| Kaneriya 2016 | REM | practice | DSM IV | Venlafaxine + Aripiprazole | Venlafaxine | Regression | 12 | [Lenze et al. (2015)](#_ENREF_77) |
| Katon 2010 | REM | practice | DSM IV | Care management + activities + Problem Solving in Primary Care | Usual care | Regression | 96† | [Unutzer et al. (2002)](#_ENREF_144) |
| Kin 1997 | RES | practice | DSM III | Moclobemide | Nortriptyline / Placebo | Bivariate | 7 | [Nair et al. (1995)](#_ENREF_99) |
| Kok 2009a | REM | practice | DSM IV | Venlafaxine | Nortriptyline | Survival analysis | 12 | [Kok et al. (2007)](#_ENREF_66) |
| Kok 2009b | REM | practice | DSM IV | Venlafaxine | Nortriptyline | ROC analysis | 12 | [Kok et al. (2007)](#_ENREF_66) |
| Koran 1995 | RES/REM | practice | DSM III R | Fluoxetine | Placebo | Regression | 6 | Primary |
| Korte 2012 | SCORE | practice | MINI | Life review therapy | Usual care | Regression | 36 | [Korte et al. (2009)](#_ENREF_71) |
| Krahn 2006 | SCORE | practice | MINI | Integrated care | Enhanced specialty referral | Regression | 24 | [Levkoff et al. (2004)](#_ENREF_78)  |
| Krishnan 2001 | RES | practice | DSM III R | Sertraline/Nortriptyline | Placebo | Regression | 12 | Bondareff et al. (2000), Newhouse et al. (2000) (Bondareff et al. (2000); Newhouse et al. (2000)) |
| Laidlaw 2008 | SCORE | practice | DSM IV | CBT | Usual care | ANCOVA | 24† | Primary |
| Mavandadi 2007 | SCORE | practice | DSM IV | Integrated care | Specialty referral care | Regression | 52† | [Krahn et al. (2006a)](#_ENREF_72) |
| Morse 2005 | RES | practice | SADS | Nortriptyline+ IPT | Placebo | Survival analysis | 26 | [Reynolds et al. (1999)](#_ENREF_118) |
| Mulsant 2001 | RES | practice | DSM IV | Nortriptyline | Paroxetine | Regression | 12 | [Mulsant et al. (1999)](#_ENREF_95) |
| Murphy 2013 | SCORE | practice | DSM IV | Mirtazapine | Paroxetine | Principal component | 8 | [Schatzberg et al. (2002)](#_ENREF_129) |
| Narushima 2010 | RES | mixed | DSM IV TR | rTMS | Placebo | Regression | 2 | Primary |
| Navarro 2001 | REM | practice | DSM IV | Citalopram | Nortriptyline | Bivariate | 12 | Primary |
| Rapaport 2003 | SCORE | practice | DSM IV | Paroxetine CR/ Paroxetine IR | Placebo | Regression | 12 | Primary |
| Raskin 2008 | RES | practice | DSM IV | Duloxetine | Placebo | Survival analysis | 8 | [Raskin et al. (2007)](#_ENREF_114) |
| Riebe 2012 | RES | practice | DSM IV | Care management + Activities + Problem Solving in Primary Care | Usual care | Regression | 52† | [Unutzer et al. (2002)](#_ENREF_144) |
| Roose 2004 | RES/REM | mixed | DSM IV | Citalopram | Placebo | Regression | 8 | Primary |
| Rosenthal 2005 | SCORE | practice | DSM III R | Antidepressants+Clinical management+Dialectical behaviour therapy | Antidepressants + Clinical management | Regression | 28 | [Lynch et al. (2003)](#_ENREF_82) |
| Salloway 2002 | SCORE | practice | DSM IV | Sertraline (old) / Citalopram (very old) | Placebo | Bivariate | 8 | [Schneider et al. (2003)](#_ENREF_130) |
| Sarginson 2010a | RES | practice | DSM IV | Mirtazapine | Paroxetine | Regression | 8 | Murphy et al. (2003), Schatzgerg et al. (2002) (Murphy et al. (2003); Schatzberg et al. (2002)) |
| Sarginson 2010b | REM | practice | DSM IV | Mirtazapine | Paroxetine | Regression | 8 | Murphy et al. (2003), Schatzgerg et al. (2002) (Murphy et al. (2003); Schatzberg et al. (2002)) |
| Schweizer 1998 | SCORE | practice | DSM III R | Buspirone / Imipramine | Placebo | Factorial analysis | 8 | Primary |
| Singh 1997 | SCORE | community | DSM IV | High intensity progressive resistance training | Interactive health education program | Regression | 10 | Primary |
| Smagula 2016 | SCORE | practice | DSM IV | Venlafaxine + Aripiprazole | Venlafaxine + Placebo | Bivariate | 12 | [Lenze et al. (2015)](#_ENREF_77) |
| Small 1995 | SCORE | practice | DSM III R | Fluoxetine | Placebo | Regression | 6 | [Tollefson et al. (1995)](#_ENREF_143) |
| Sneed 2007 | SCORE | community | DSM IV | Citalopram | Placebo | Regression | 8 | [Roose et al. (2004a)](#_ENREF_122) |
| Sneed 2008 | RES | practice | DSM IV | Citalopram | Placebo | Regression | 8 | [Roose et al. (2004a)](#_ENREF_122) |
| Sneed 2011 | REM | mixed | DSM IV | Sertraline | Nortriptyline | Regression | 12 | Primary |
| Steffens 2006 | SCORE | practice | DSM IV | Care management + Activities + Problem Solving in Primary Care | Usual care | Regression | 96† | [Unutzer et al. (2002)](#_ENREF_144) |
| Tan 1994 | SCORE | practice | N/A | Iofepramine | Placebo | Bivariate | 5 | Primary |
| van Schaik 2006 | RES | practice | PRIME-MD | IPT | Usual care | Regression | 24 | Primary |
| Volz 1995 | CAT | practice | DSM III | Brofaromine | Imipramine | Bivariate | 8 | Moller and Volz (1992,1993) (Moller and Volz (1992), 1993)) |
| Zanetidou 2016 | REM | practice | DSM IV | Sertraline + Physical exercise | Sertraline | Regression | 24† | [Belvederi M. et al. (2015)](#_ENREF_19) |

*Note:*

*Outcome* RES = response, REM = remission, SCORE = score on depression questionnaire, CAT = depression categories (e.g. high persistent, high decline and low decline)

*Diagnostic criteria* DSM = Diagnostic and Statistical Manual of Mental Disorders, PRIME-MD = Primary Care Evaluation of Mental Disorders screening questionaire for depressive symptoms, MINI = The M.I.N.I. International Neuropsychiatric Interview, SADS= Schedule for Affective Disorders and Schizophrenia-Lifetime Version, GMS/AGECAT = Geriatric Mental Scale/AGECAT

*Intervention* CBT = Cognitive behavioural therapy, IPT = Interpersonal psychotherapy, ECT= Electroconvulsive therapy, rTMS = repetitive Transcranial Magnetic Stimulation

† = data calculated from months or years to weeks by multiply by 4 and 52, respectively.

**Table 3: Statistically significant predictors of response, remission and depression score or category**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Factors** | **Predictors** |  | **Response** |  | **Remission** |  | **Score/Category** |
| *Demographic* |  |  |  |  |
| Ethnic | Black | +  | Ackerman 1997a Ackerman 2000a |  |  |  |  |
|  | White |  |  |  |  | + | Bao 2011c Smagula 2016a |
| Age | Older age |  |  | + | Zanetidou 2016d | + | Bogner 2012c |
|  |  | - | Jorge 2008d | - | Riebe 2012c | - | Bondareff 2000a Chan 2013b |
| Gender | Female | - | Raskin 2008a | - | Raskin 2008a |  |  |
| Marital status | Being married | + | Bogner 2012c |  |  | - | Lailaw 2008b |
| Education | Higher level |  |  |  |  | + | Gilman 2013c |
|  |  |  |  |  |  | - | Bao 2011c |
| Socioeconomic | Financial strain |  |  |  |  | - | Gilman 2013c |
|  | Social support |  |  |  |  | + | Gilman 2013c |
|  |  |  |  |  |  |  |  |
| *Clinical* |  |  |  |  |  |  |  |
| Depression | Baseline severity | + | Roose 2004avan Schaik 2006b |  |  | + | Tan 1994a |
|  |  | - |  Mulsant 2001a  | - | Ackerman 1997aAlexopoulos 2005cAzar 2011c Bjolseth 2015d Capaeliez 2007c Ghesquier 2014c Katon 2010c Kok 2009aaRaskin 2008a | - | Banerjee 1996cCoon 2007b Mavandadi 2007c Rosenthal 2005b |
|  | Early improvement | + | Koran 1995aKok 2009ba | + | Koran 1995a | + | Volz 1995a |
|  | Current episode duration | - | Mulsant 2001a | - | Kok 2009aa | - | Rapaport 2003a |
|  | Severe group (endogenous, psychotic, severe inhibition) |  |  | + | Navarro 2001a |  |  |
|  | Age of initial onset |  |  |  |  | + | Rosenthal 2005b |
|  | First episode |  |  |  |  | - | Banerjee 1996c |
|  | Previous antidepressant failure |  |  | - | Hsu 2016a |  |  |
| Anxiety | Baseline severity | - | Ackerman 2000a Andreescu 2007abc  | - | Ackerman 1997a Alexopoulos 2005c Azar 2011c Kaneriya 2016a Zanetidou 2016d |  |  |
|  | Severity at 6 week of treatment |  |  | - | Greenlee 2010b |  |  |
|  | Worry and panic | - | Andreescu 2009abc |  |  |  |  |
| Other symptoms | Psychotic | - | Bjolseth 2015d | + | Bjolseth 2015d |  |  |
|  | Suicidal ideation |  |  |  |  | - | Bogner 2012c |
|  | Psychomotor retardation |  |  | + | Zanetidou 2016d |  |  |
|  | Somnolence | + | Ackerman 2000a |  |  |  |  |
|  | Somatisation | - | Ackerman 1997a |  |  |  |  |
|  | Somatic symptoms |  |  | - | Cappeliez 2007c |  |  |
|  | Hopelessness |  |  | - | Alexopoulos 2005c |  |  |
|  | Limitation of emotional function |  |  | - | Alexopoulos 2005c |  |  |
|  | Perceived adequacy of emotional and instrumental support | + | Cappeliez 2007c |  |  |  |  |
|  | Engagement in pleasant activity |  |  | + | Riebe 2012c |  |  |
| *Personality* | Cluster C personality disorder | - | Morse 2005abc |  |  |  |  |
|  | Extraversion trait |  |  |  |  | + | Korte 2012b |
|  |  |  |  |  |  |  |  |
| *Physical* | Physical illness | -  | Evans 1997a | - | Alexopoulos 2005cAzar 2011c | - | Bogner 2012cChan 2014b Gilman 2013c Krahn 2006c |
|  | Pain |  |  | - | Raskin 2008a | - | Mavandadi 2007c |
|  | Cerebrovascular disease | - | Evans 1997a Raskin 2008a |  |  |  |  |
|  | Polypharmacy |  |  | + | Zanetidou 2016d |  |  |
|  | Headache | + | Ackerman 2000a |  |  |  |  |
|  |  |  |  |  |  |  |  |
|  | Limitation of physical function |  |  | - | Alexopoulos 2005c |  |  |
|  | Dyspnea-related disability |  |  |  |  | - | Alexopoulos 2014c |
|  | Maximum Oxygen uptake (VO2max) |  |  | + | Zanetidou 2016d |  |  |
| *Investigation* |  |  |  |  |  |  |  |
| Blood | Bupropion plasma concentration | + | Adeoye 2000 a |  |  |  |  |
|  | Erythrobupropion and threobupropion | - | Adeoye 2000 a |  |  |  |  |
|  | Folic level |  |  |  |  | + | Alpert 2003 a |
|  | Cortisol level | - | Kin 1997a |  |  |  |  |
|  | Dexamethasone suppression test: suppressor | + | Kin 1997 a |  |  |  |  |
| EEG | Low-theta power in subgenual ACC cluster | + | Narushima 2010d |  |  |  |  |
| Genetic | rs1360780 | - |  Sarginson 2012b a |  |  |  |  |
|  | rs3800373 | - |  Sarginson 2012b a |  |  |  |  |
|  | rs2032583 C carrier |  |  | + |  Sarginson 2012a a |  |  |
|  | rs2235040 A carrier |  |  | + |  Sarginson 2012a a |  |  |
|  | BDNF variant |  |  |  |  | ? | Murphy 2013 a |
|  | CREB1 variant |  |  |  |  | ? | Murphy 2013 a |
|  | HLA-DRB5 |  |  | ? | Eyre 2016 a |  |  |
|  | SELENBP1 |  |  | ? | Eyre 2016 a |  |  |
|  | LOC388588 |  |  | ? | Eyre 2016 a |  |  |
| *Neuropsychological* |  |  |  |  |  |  |  |
| General cognition  | MMSE >23 | + | Evans 1997 a |  |  |  |  |
|  | Cognitive decline |  |  |  |  | - | Steffens 2006c |
|  | Attention |  |  |  |  | + | Smagula 2016 a |
|  | Immediate memory |  |  |  |  | + | Smagula 2016 a |
| Executive function | Response inhibition in Stroop | - | Bogner 2007c | - | Bogner 2007c | - | Sneed 2007 a |
|  | Trail Making Test :set shifting | + | Beaudreau 2015b | + | Kaneriya 2016 a | + | Smagula 2016 a |
|  |  |  |  |  |  |  |  |
| *Brain imaging* |  |  |  |  |  |  |  |
|  | Deep white matter hyperintensity | - | Sneed 2011 a |  |  |  |  |
|  | Periventricular hyperintensity | - | Sneed 2011 a |  |  |  |  |
|  | Total hyperintensity volume | - | Sneed 2011 a |  |  |  |  |
|  | Gray matter volume in left and right frontal brain region |  |  | + | Jorge 2008d |  |  |

*Note:* + = positive prediction to outcome, - = negative prediction to outcome, ? = direction of prediction to outcome was not identified.
Subscript: a= pharmacologic study, b=psychological therapy study, c= care management study, d= rTMS or ECT study, abc= combined pharmacotherapy, psychological and care management study.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Predictor | Study | Pooled OR | 95% CI | z | p | Q | p | I2(%) | Tau2 | Eggerbias estimate | 95% CI | p |
| Age | 6 | 0.783 | 0.457 | 1.342 | -0.888 | 0.374 | 24.31 | <.001 | 79.4 | 0.3102 | -0.633 | -3.668 | 2.403 | 0.594 |
| Baseline anxiety | 7 | 0.447 | 0.271 | 0.736 | -3.163 | 0.002 | 32.70 | <.001 | 81.7 | 0.2752 | 2.467 | -3.093 | -1.841 | <0.001 |
| Baseline depression | 14 | 0.886 | 0.833 | 0.943 | -3.828 | <0.001 | 75.97 | <.001 | 82.9 | 0.0053 | -1.648 | -3.111 | -0.185 | 0.030 |
| Trail making test | 3 | 2.247 | 1.405 | 3.593 | 3.381 | 0.001 | 1.23 | 0.540 | 0.0 | 0.0000 | 0.944 | -9.759 | 11.647 | 0.464 |
| Physical illness | 5 | 0.843 | 0.712 | 0.998 | -1.980 | 0.048 | 35.62 | <.001 | 88.8 | 0.0208 | -2.950 | -5.777 | -0.123 | 0.045 |

**Table 4: Results of meta-analysis for each predictor variable of good outcome.**

**Table 5: Results of subgroup meta-analyses by treatment type for each predictor.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Predictor *Treatment type* | No. of study | Pooled OR (95% CI) | Overall effect: z (p value) | I2 % (p value) | Publication bias: Eggerbias estimate (p value) | Subgroup differences†:I2 (p value) |
| **Age** |  |  |  |  |  | 82.9 (0.003) |
|  *Biological* | 3 | 0.447 (0.221, 0.903) | 2.24(0.025) | 59.3 (0.086) | -0.355 (0.976) |  |
|  *Psychosocial* | 1 | 0.973 (0.457, 1.342) | 0.04 (0.970) | 87.0 (0.006) | N/A |  |
|  *Biological plus psychosocial* | 2 | 1.428 (0.593, 3.440) | 0.79 (0.427) | N/A | UC |  |
|  |  |  |  |  |  |  |
| **Baseline depression** |  |  |  |  |  | 86.0 (0.001) |
|  *Biological* | 5 | 0.786 (0.575, 1.075) | 1.51 (0.132) | 85.1 (<0.001) | -0.719 (0.709) |  |
|  *Psychosocial* | 2 | 0.472 (0.187, 1.192) | 1.59 (0.112) | 49.5 (0.159) | UC |  |
|  *Biological plus psychosocial* | 7 | 0.922 (0.874, 0.973) | 2.98 (0.003) | 81.8 (<0.001) | -2.182 (0.065) |  |
|  |  |  |  |  |  |  |
| **Baseline anxiety** |  |  |  |  |  | 94.5 (<0.001) |
|  *Biological* | 4 | 0.273 (0.154, 0.484) | 4.44 (<0.001) | 0 (0.752) | -1.346 (0.311) |  |
|  *Psychosocial* | 0 | N/A | N/A | N/A | N/A |  |
|  *Biological plus psychosocial* | 3 | 0.656 (0.399, 1.079) | 1.66 (0.097) | 85.1 (0.001) | -2.941 (0.052) |  |
|  |  |  |  |  |  |  |
| **Physical illness** |  |  |  |  |  | 95.5 (<0.001) |
|  *Biological* | 0 | N/A | N/A | N/A | N/A |  |
|  *Psychosocial* | 1 | 0.016 (0.003, 0.089) | 4.76 (<0.001) | N/A | N/A |  |
|  *Biological plus psychosocial* | 4 | 0.900 (0.808, 1.002) | 1.91 (0.056) | 77.6 (0.004) | -2.147 (0.115) |  |
|  |  |  |  |  |  |  |
| **Executive functioning (Trail Making Test)** |  |  |  |  |  | 18.0 (0.269) |
|  *Biological* | 2 | 2.080 (1.276, 3.391) | 2.94 (0.003) | 0 (0.930) | UC |  |
|  *Psychosocial* | 1 | 5.571 (1.042, 29.790) | 2.01 (0.045) | N/A | UC |  |
|  *Biological plus psychosocial* | 0 | N/A | N/A | N/A | N/A |  |
|  |  |  |  |  |  |  |

Note: *Biological treatment type* consisted of data from pharmacological trials and rTMS/ECT trials.

 *Psychosocial treatment type* consisted of data from psychological treatment trials.

 *Biological plus psychosocial* treatment type consisted of data from care management and combined treatment trials.

 † Overall test for heterogeneity between subgroup. Bonferroni-corrected alpha level of 0.01, adjusted for the number of treatment type subgroup analyses.

 N/A is for not available. UC is for unable to calculate.

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