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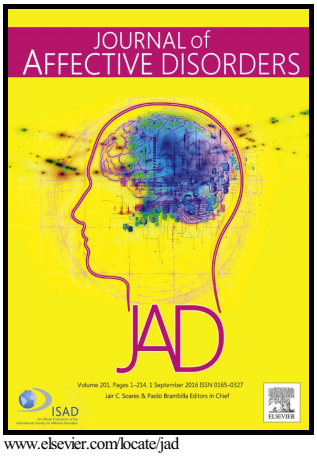

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Predictors of treatment outcome in depression in later life: a systematic review and meta-analysis

Authors

Chavit Tunvirachaisakul[1,4*], Rebecca L. Gould[1,2], Mark C. Coulson[3], Emma V. Ward[3], Gemma Reynolds[3], Rebecca L. Gathercole[1], Hannah Grocott[1], Thitiporn Supasitthumrong[4], Athicha Tunvirachaisakul[5], Kate Kimona[2], Robert J. Howard[1,2]

[1]Department of Old Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

[2]Division of Psychiatry, University College London, London, UK

[3]Department of Psychology, Faculty of Science and Technology, Middlesex University, London, UK

[4]Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

[5]Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand

chavit.tunvirachaisakul@kcl.ac.uk

chavit.t@chula.ac.th

***Corresponding author.** Chavit Tunvirachaisakul, Tel.: +44 (0)20 7848 0626 (UK), +66(0)2 256 4298 (TH), Department of Old Age Psychiatry, IoPPN, King's College London, Box PO70, De Crespigny Park, Denmark Hill, London, UK SE5 8AF, Department of Psychiatry, King Chulalongkorn Memorial Hospital, 1873 Rama IV Road Bangkok, Thailand, 10330

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Abstract

Background

Predictor analyses of late-life depression can be used to identify variables associated with outcomes of treatments, and hence ways of tailoring specific treatments to patients. The aim of this review was to systematically identify, review and meta-analyse predictors of outcomes of any type of treatment for late-life depression.

Methods

Pubmed, Embase, CINAHL, Web of Science and PsycINFO were searched for studies published up to December 2016. Primary and secondary studies reported treatment predictors from randomised controlled trials of any treatment for patients with major depressive disorder aged over 60 were included. Treatment outcomes included response, remission and change in depression score.

Results

Sixty-seven studies met the inclusion criteria. Of 65 identified statistically significant predictors, only 7 were reported in at least 3 studies. Of these, 5 were included in meta-analyses, and only 3 were

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statistically significant. Most studies were rated as being of moderate to strong quality and satisfied key quality criteria for predictor analyses.

Limitations

The searches were limited to randomised controlled trials and most of the included studies were secondary analyses.

Conclusions

Baseline depression severity, co-morbid anxiety, executive dysfunction, current episode duration, early improvement, physical illnesses and age were reported as statistically significant predictors of treatment outcomes. Only the first three were significant in meta-analyses. Subgroup analyses showed differences in predictor effect between biological and psychosocial treatment. However, high heterogeneity and small study numbers suggest a cautious interpretation of results. These predictors were associated with various mechanisms including brain pathophysiology, perceived social support and proposed distinct types of depressive disorder. Further investigation of the clinical utility of these predictors is suggested.

Keywords: Systematic review, meta-analysis, predictor, late-life depression, major depressive disorder.

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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). 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). 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) 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) 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),

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but not demographic or clinical variables, were associated with the magnitude of treatment outcome. In a patient-level meta-analysis, Nelson et al. (2013) 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) 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) 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) 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) 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). 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.

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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) 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; Pincus et al., 2011; Sun et al., 2012) . 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

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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). 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), and then converted to odds ratio using Hasselblad and Hedges' method (Hasselblad and Hedges, 1995). This has been shown to be the most robust method for this type of effect size conversion (da Costa et al., 2012) .

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). 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 I^2 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). Publication bias was estimated using Egger's regression asymmetry test, which is suitable for small numbers of studies (Egger et al., 1997). If publication bias

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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) . 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

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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).

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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), 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) 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) also reported that frontal lobe atrophy with advancing age reduced the effect of rTMS treatment. Further, Ribeiz et al. (2013) 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.

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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.

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Several possibilities have been suggested to explain this association. First, Ackerman et al. (1997) commented that it is easier to reach an endpoint if you start with a lower baseline score of depression. Second, Nasser and Overholser (2005) 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; Roose et al., 2004a).

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) 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) 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) 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.

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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) suggested that the predictive value of early improvement on treatment outcome may be small. Rodin and Voshart (1986) 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) 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

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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; Calati et al., 2013; Goodkind et al., 2016; Moller et al., 2010; Pimontel et al., 2012). Keller et al. (1986) 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; Moller et al., 2010; Pimontel et al., 2012). Although, Nelson et al. (2009) 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; Morimoto et al., 2011), more recent brain imaging studies have showed more distinct features between depression alone and depression with anxiety symptoms. For example, Canu et al. (2015) 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) suggested that anxiety may be associated with smaller cortical thickness in the elderly. Furthermore, Domschke et al. (2010) found that the neuropeptide Y gene, which was found in anxious depressed patients, affected antidepressant treatment response, and Baffa et al. (2010) 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) 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.

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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; Marson et al., 1997). 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; Rodin and Voshart, 1986). 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). 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). 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). 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). A cohort study showed that Wisconsin Card Sorting Test, but not

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verbal fluency or Stroop test, was associated with response to cognitive behavioural treatment (Goodkind et al., 2016). 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; Alexopoulos et al., 2002). Furthermore, the impairment was linked to lower frontal subcortical and limbic volume. Patel et al. (2015) 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) 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). Furthermore, 67% of included studies were secondary analyses, which questions the

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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.

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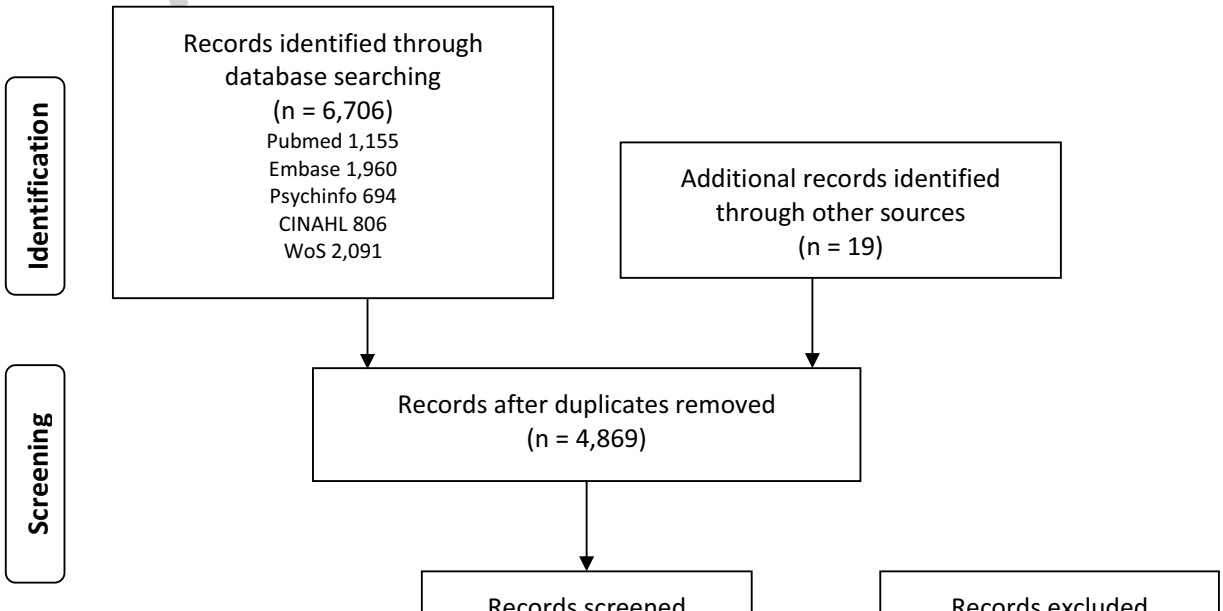
Figure 1: PRISMA Flow Diagram



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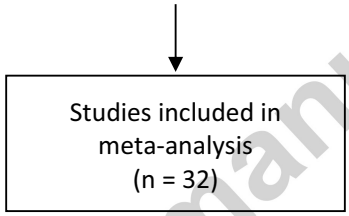

Adapted from: Moher et al. (2009)

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

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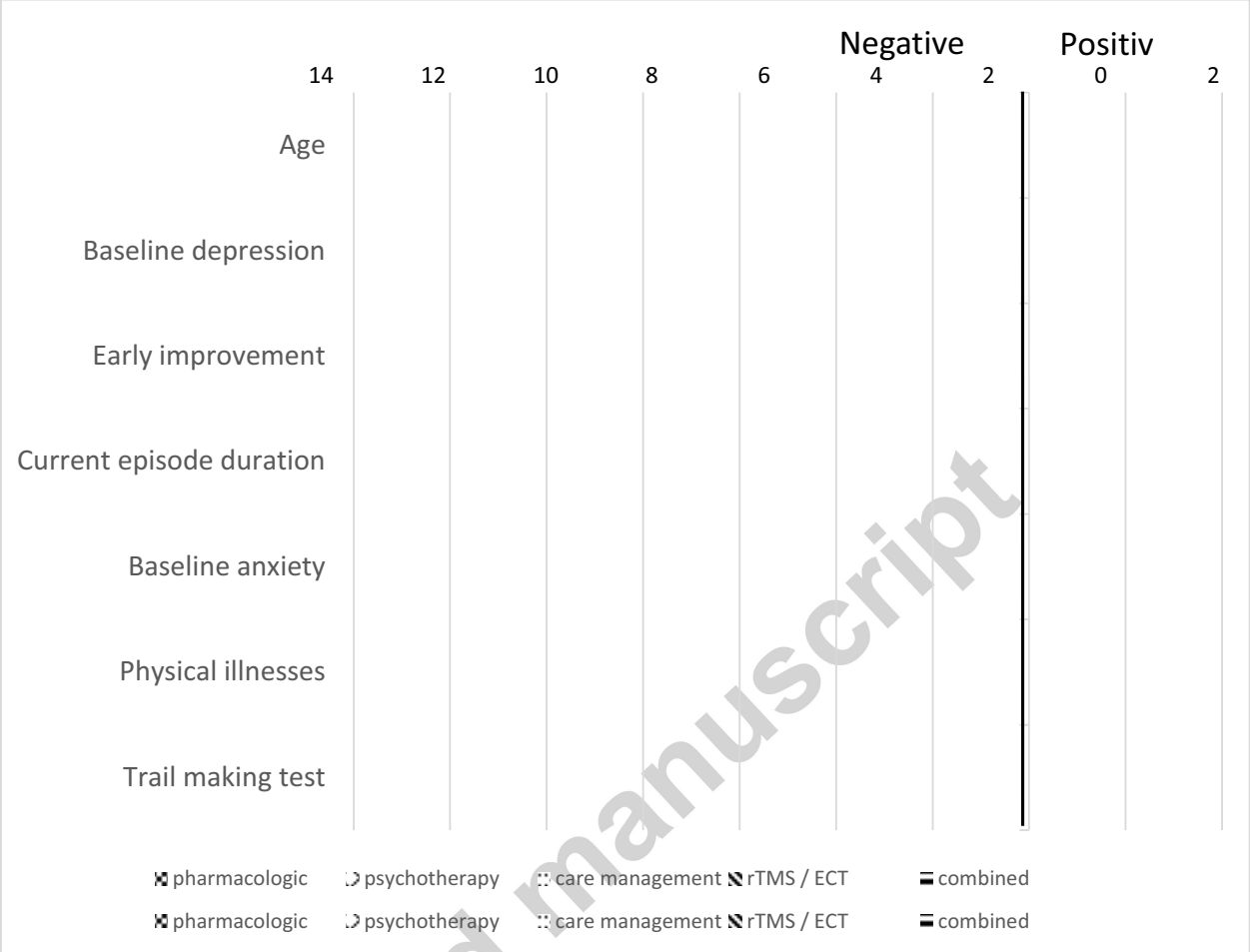

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Figure 3: Forest plot of each predictors included in the meta-analysis

Table 1: Demographic and clinical characteristics

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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	HAMD17	15	20.64	61.94	109.38

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						/A)					
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 cli	SCL-20	N/A	1.675	N/A	N/A

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						nical judgment (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 (2	HAMD17	15	22.1	N/A	22

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						8.1)					
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 multicentres	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)	HAMD17	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	95	69.68	N/A	70.34	N/A	MMSE	HAMD1	18	23.5	N/A	N/A

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centres						(28.68)	7			
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

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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 2001 US	116	72.1	N/A	71.6	86.2	MMSE (56.5)	HAMD17	15	22.4	60.6	26
Murphy 2013 US	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 cogniti	SCL-20	N/A	*	N/A	N/A

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						screener (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
Sallaway 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	HAMD17	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

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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 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 (26.8	HAMD17	18	20.14	N/A	N/A

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					7)			

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)
Ackerman 2000	RES/REM	practice	DSM III R	Fluoxetine	Placebo	Regression	6	Tollefson et al. (1995)
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)
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)
Andrescu	RES	practic	DSM IV	Pharmacotherapy + Clinical management /	Placebo	Survival	12	Reynolds et al. (2006)

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2007		e		Placebo + Clinical management / Pharmacotherapy + IPT / Placebo + IPT		analysis	0	
Andreescu 2009	RES	practice	DSM IV	Pharmacotherapy + Clinical management / Placebo + Clinical management / Pharmacotherapy + IPT / Placebo + IPT	Placebo	Bivariate	104†	Reynolds et al. (2006)
Azar 2011	REM	practice	DSM IV	Integrated care model	Enhance specialty referral model	Regression	24†	Krahn et al. (2006a)
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)
Beaudreau 2015	RES/REM	practice	DSM IV	Problem solving therapy	Supportive therapy	ROC analysis	12	Arean et al. (2010)
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)
Bogner 2012	CAT	practice	DSM IV	Care management	Usual care	Regression	96†	Bruce et al. (2004)
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	SCOR	practic	RDC	CBT + Desipramine	CBT alone	Regression	16	Thompson et al. (2001)

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	E	e					†	
Evans 1997	RES	practice	GMS / AGECAT	Fluoxetine	Placebo	Regression	8	Evans et al. (1997a)
Eyre 2016	REM	practice	DSM IV	Methylphenidate + Citalopram	Methylphenidate / Citalopram	Bivariate	16	Lavretsky et al. (2015)
Fields 2012	SCORE	practice	not specified	Celecoxib/ Naproxen sodium	Placebo	Regression	260†	Lyketsos et al. (2007)
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)
Gildengers 2002	RES	practice	DSM IV	Paroxetine	Nortriptyline	Regression	12	Reynolds et al. (1999)
Gilman 2013	SCORE	practice	DSM IV	Care management	Usual care	Regression	104†	Bruce et al. (2004)
Greenlee 2010	REM	practice	DSM IV	IPT + Care management	Care management	Survival analysis	16	Reynolds et al. (2010)
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)
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)
Katon 2010	REM	practice	DSM IV	Care management + activities + Problem Solving in Primary Care	Usual care	Regression	96†	Unutzer et al. (2002)
Kin 1997	RES	practice	DSM III	Moclobemide	Nortriptyline / Placebo	Bivariate	7	Nair et al. (1995)
Kok 2009a	REM	practice	DSM IV	Venlafaxine	Nortriptyline	Survival analysi	12	Kok et al. (2007)

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						s		
Kok 2009b	REM	practice	DSM IV	Venlafaxine	Nortriptyline	ROC analysis	12	Kok et al. (2007)
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)
Krahn 2006	SCORE	practice	MINI	Integrated care	Enhanced specialty referral	Regression	24	Levkoff et al. (2004)
Krishnan 2001	RES	practice	DSM III R	Sertraline/Nortriptyline	Placebo	Regression	12	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)
Morse 2005	RES	practice	SADS	Nortriptyline+ IPT	Placebo	Survival analysis	26	Reynolds et al. (1999)
Mulsant 2001	RES	practice	DSM IV	Nortriptyline	Paroxetine	Regression	12	Mulsant et al. (1999)
Murphy 2013	SCORE	practice	DSM IV	Mirtazapine	Paroxetine	Principal component	8	Schatzberg et al. (2002)
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)
Riebe 2012	RES	practice	DSM IV	Care management + Activities + Problem Solving in Primary Care	Usual care	Regression	52†	Unutzer et al. (2002)

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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)
Salloway 2002	SCORE	practice	DSM IV	Sertraline (old) / Citalopram (very old)	Placebo	Bivariate	8	Schneider et al. (2003)
Sarginson 2010a	RES	practice	DSM IV	Mirtazapine	Paroxetine	Regression	8	Murphy et al. (2003), Schatzgerg et al. (2002)
Sarginson 2010b	REM	practice	DSM IV	Mirtazapine	Paroxetine	Regression	8	Murphy et al. (2003), Schatzgerg 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)
Small 1995	SCORE	practice	DSM III R	Fluoxetine	Placebo	Regression	6	Tollefson et al. (1995)
Sneed 2007	SCORE	community	DSM IV	Citalopram	Placebo	Regression	8	Roose et al. (2004a)
Sneed 2008	RES	practice	DSM IV	Citalopram	Placebo	Regression	8	Roose et al. (2004a)
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)
Tan 1994	SCORE	practice	N/A	Iofepramine	Placebo	Bivariate	5	Primary
van Schaik 2006	RES	practice	PRIME-MD	IPT	Usual care	Regression	24	Primary

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Volz 1995	CAT	practice	DSM III	Brofaromine	Imipramine	Bivariate	8	Moller and Volz (1992,1993)
Zanetidou 2016	REM	practice	DSM IV	Sertraline + Physical exercise	Sertraline	Regression	24 †	Belvederi M. et al. (2015)

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 1997[a] Ackerman 2000[a]		
	White			+ Bao 2011[c] Smagula 2016[a]
Age	Older age		+ Zanetidou 2016[d]	+ Bogner 2012[c]
		- Jorge 2008[d]	- Riebe 2012[c]	- Bondareff 2000[a] Chan 2013[b]
Gender	Female	- Raskin 2008[a]	- Raskin 2008[a]	

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Marital status	Being married	+	Bogner 2012[c]			-	Lailaw 2008[b]
Education	Higher level					+	Gilman 2013[c]
						-	Bao 2011[c]
Socioeconomic	Financial strain					-	Gilman 2013[c]
	Social support					+	Gilman 2013[c]
Clinical							
Depression	Baseline severity	+	Roose 2004[a] van Schaik 2006[b]			+	Tan 1994[a]
		-	Mulsant 2001[a]	-	Ackerman 1997[a] Alexopoulos 2005[c] Azar 2011[c] Bjolseth 2015[d] Capaeliez 2007[c] Ghesquier 2014[c] Katon 2010[c] Kok 2009a[a] Raskin 2008[a]	-	Banerjee 1996[c] Coon 2007[b] Mavandadi 2007[c] Rosenthal 2005[b]
	Early improvement	+	Koran 1995[a] Kok 2009b[a]	+	Koran 1995[a]	+	Volz 1995[a]
	Current episode duration	-	Mulsant 2001[a]	-	Kok 2009a[a]	-	Rapaport 2003[a]
	Severe group (endogenous, psychotic, severe inhibition)			+	Navarro 2001[a]		

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	Age of initial onset				+	Rosenthal 2005[b]
	First episode				-	Banerjee 1996[c]
	Previous antidepressant failure			-	Hsu 2016[a]	
Anxiety	Baseline severity	-	Ackerman 2000[a] Andreescu 2007[abc]	-	Ackerman 1997[a] Alexopoulos 2005[c] Azar 2011[c] Kaneriya 2016[a] Zanetidou 2016[d]	
	Severity at 6 week of treatment			-	Greenlee 2010[b]	
	Worry and panic	-	Andreescu 2009[abc]			
Other symptoms	Psychotic	-	Bjolseth 2015[d]	+	Bjolseth 2015[d]	
	Suicidal ideation				-	Bogner 2012[c]
	Psychomotor retardation			+	Zanetidou 2016[d]	
	Somnolence	+	Ackerman 2000[a]			
	Somatisation	-	Ackerman 1997[a]			
	Somatic symptoms			-	Cappeliez 2007[c]	
	Hopelessness			-	Alexopoulos 2005[c]	
	Limitation of emotional function			-	Alexopoulos 2005[c]	
	Perceived adequacy of emotional and	+	Cappeliez			

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	instrumental support		Evans 2007[c]				
	Engagement in pleasant activity			+	Riebe 2012[c]		
Personality	Cluster C personality disorder	-	Morse 2005[abc]				
	Extraversion trait					+	Korte 2012[b]
Physical	Physical illness	-	Evans 1997[a]	-	Alexopoulos 2005[c] Azar 2011[c]	-	Bogner 2012[c] Chan 2014[b] Gilman 2013[c] Krahn 2006[c]
	Pain			-	Raskin 2008[a]	-	Mavandadi 2007[c]
	Cerebrovascular disease	-	Evans 1997[a] Raskin 2008[a]				
	Polypharmacy			+	Zanetidou 2016[d]		
	Headache	+	Ackerman 2000[a]				
	Limitation of physical function			-	Alexopoulos 2005[c]		
	Dyspnea-related disability					-	Alexopoulos 2014[c]
	Maximum Oxygen uptake (VO2max)			+	Zanetidou 2016[d]		
Investigation							
Blood	Bupropion plasma concentration	+	Adeoye 2000[a]				
	Erythrobupropion and threobupropion	-	Adeoye 2000[a]				

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	Folic level				+	Alpert 2003 [a]
	Cortisol level	-	Kin 1997 [a]			
	Dexamethasone suppression test: suppressor	+	Kin 1997 [a]			
EEG	Low-theta power in subgenual ACC cluster	+	Narushima 2010 [d]			
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 2006 [c]
	Attention				+	Smagula 2016 [a]
	Immediate memory				+	Smagula 2016 [a]
Executive function	Response inhibition in Stroop	-	Bogner 2007 [c]	-	Bogner 2007 [c]	- Sneed 2007 [a]
	Trail Making Test :set shifting	+	Beaudreau 2015 [b]	+	Kaneriya 2016 [a]	+ Smagula 2016 [a]

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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 2008 d	

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.

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

Predictor	Study	Pooled OR	95% CI		z	p	Q	p	I^2 (%)	Tau^2	Egger bias 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 depress	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

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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)	I^2 % (p value)	Publication bias: Egger bias estimate (p value)	Subgroup differences†: I^2 (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	4	0.900	1.91	77.6	-2.147	

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psychosocial		(0.808, 1.002)	(0.056)	(0.004)	(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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Author Disclosure

Author contribution

CT, RLGo and RH participate in study design, analysis and article preparation. CT, RLGo, RLGa, HG, MC, EW, GR, TS and AT reviewed, extracted data and assessed quality of the included articles. CT and KK extracted data for meta-analysis. All the co-authors substantially contributed to this review and approving it for the submission.

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Highlights

- Older age and executive functioning impairment predicted poor outcome.
- Presence of co-morbid anxiety and physical illnesses also predicted poor outcome.
- Lower baseline depression severity, shorter episode duration and early improvement predicted good outcome.
- Meta-analysis confirmed baseline depression, anxiety and TMT associated with outcome.
- Subgroup analyses revealed treatment specific predictor, but with limitation.

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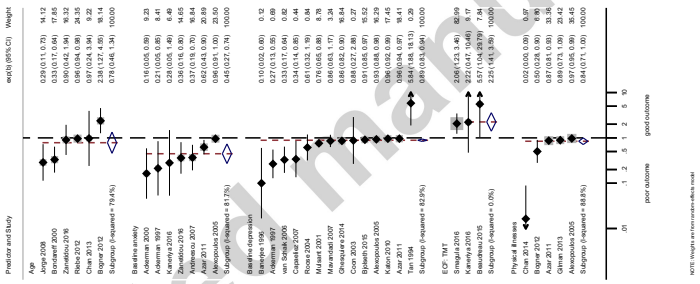

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