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Psychosocial Interventions for the Acute Treatment of Late-life Major Depression: A Systematic Review of Evidence-based Treatments, Predictors of Treatment Outcomes and Moderators of Treatment Effects

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Abstract

The goal of this systematic review is to evaluate the efficacy of psychosocial interventions for the acute treatment of late-life depression and identify predictors of treatment outcomes and moderators of treatment effects. The results of the systematic review may help to advance the development of personalized psychosocial treatments for late-life major depression. Based on our criteria, Problem Solving Therapy (PST), Cognitive Behavioral Therapy (CBT), and Treatment Initiation and Participation Program (TIP) have *supportive evidence of efficacy, pending replication*. Even though the data on the predictors of treatment outcomes and moderators of treatment effects are still preliminary, it appears that baseline anxiety and stress level, personality pathology, endogenous depression, and reduced self-rated health are associated with worse depression outcomes. More research is also recommended to examine the moderating effects of baseline depression severity; for instance, our review indicates that Interpersonal Psychotherapy (IPT) may work better in participants with high baseline depression severity than in participants with low depression severity. Recommendations for future novel psychosocial interventions for the acute treatment of late-life major depression include application of these interventions in non-traditional settings, involvement of the caregivers in the treatment of cognitively and functionally impaired older adults with major depression, and expansion of research to include more racially and ethnically diverse populations as the samples of the examined studies is highly selective, i.e. overly healthy, cognitively intact, Caucasian, and highly educated.

INTRODUCTION

The science of interventions is shifting from adapting current interventions for different populations and settings to investing in novel, potentially more effective, personalized interventions (1). The recent *From Discovery to Cure* NIMH report on future directions for interventions research recommends that interventions researchers focus on understanding moderators of treatment response to better match patients to existing evidence based practices and to develop new interventions for those who do not respond to any existing

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treatments (2). The purpose of this paper is to review the efficacy of psychosocial interventions for the acute treatment of late-life major depression and to identify variables that predict treatment outcomes and moderate treatment effects. Based on the review of the literature as well as our scientific observations, we propose future directions that may advance the development of personalized treatments.

Our focus on major depression in this population is important for the following reasons. First, major depression interacts with and can exacerbate cognitive impairment, disability, and medical illnesses, which often occur in older adults (3). As a result, late-life major depression is associated with reduced quality of life, family disruption, high rates of utilization of medical services, and increased medical morbidity and mortality, including death from suicide (4). Moreover, compared to milder forms of late-life depression, major depression is characterized by greater severity, more persistent, difficult to treat, symptoms, greater disability, higher rates of suicidal ideation, and worse prognosis (5,6).

This is the first systematic review, to our knowledge, of psychosocial interventions for late-life major depression that also addresses questions related to personalized treatment development by examining predictors of treatment outcomes and moderators of treatment effects. Specifically, we aim to answer the following questions: Which treatments are efficacious in treating late-life major depression and which require more investigation? Which variables predict treatment outcomes and which variables moderate treatment effects of psychosocial interventions in late-life major depression? What are the necessary next steps to advance psychosocial interventions for older adults with major depression? The review may provide some guidance on the development of personalized interventions at the patient level.

METHODS

Studies were selected through searches of PUBMED (1966–2010), PsychINFO (1840–2010), Cochrane database as well through previous reviews and meta-analyses (7–22). Specifically, searches were conducted using combinations of the following keywords (the * denotes any combination of the word): “random*”, “psychother*”, “psychosoc*”, “intervention”, “older”, “predict*”, “moderat*”, “mediat*” and “elder*”. The final selection of the papers was based on those APA Division 12 criteria (23–24) that are pertinent to studies for the acute treatment of late-life major depression and additional statistical criteria regarding sample size and intent to treat analysis.

SELECTION OF STUDIES

Inclusion of RCTs—The following are the criteria for the inclusion of studies: a) a randomized clinical trial; b) a psychosocial intervention (not including interventions at the organizational level or systems-level collaborative care models); c) acute treatment of diagnosed unipolar Major Depression (MDD) (based on a diagnosis by DSM-II, DSM-III-R, DSM-IV, RDC, ICD-9 or ICD-10, Primary Care Evaluation of Mental Disorders-PRIME-MD); d) published in English; e) with an average age of participants 60 years old or older. Consistent with the recent NIMH recommendation to broaden the focus of outcome measures (25), we included RCTs that did not have a depression outcome, for example disability, quality of life, cost. Finally, we did not include articles that performed an interim analysis of an RCT because results of interim analysis are not conclusive about the efficacy of the interventions.

Initial Selection—Each study needed to meet the following American Psychological Association (APA) Division 12 (23) *study design criteria*:

- a. study clearly stated inclusion and exclusion criteria;
- b. study determined clinical as well statistical significance;
- c. a treatment manual was used;
- d. treatment fidelity was assessed or on-going supervision was provided by experts in the psychosocial interventions;
- e. reliable and valid instruments were administered;
- f. research assessments were conducted by raters unaware of the participant's randomization status (Table 1).

Final Selection—Our final selection was based on the following *statistical criteria*:

- a. the study had at least 30 participants per condition. The rationale for excluding small sample size studies is that they do not provide a meaningful estimate of the between group effect size due to the imprecision inherent in small samples, as embodied in wide confidence intervals (26). Thirty participants per arm is the minimum number to detect a Cohen's *d* of .74 effect size with 80% power (27). Our choice of 30 participants per condition is somewhat arbitrary; ideally, we would have liked to use a much larger sample size that could detect smaller yet clinically meaningful effects (28) but these studies are rarely available in late-life major depression.
- b. intent-to-treat analyses were performed. We decided to include studies that have performed intent-to-treat analyses such that they adhere to the virtue of randomization for estimating treatment effects (29).

Defining Efficacy—Efficacy was assessed based on the RCTs that met both *study design and statistical criteria*. An intervention is considered *efficacious*, if there are at least 2 RCTs, conducted by independent investigators (23–24), showing that the intervention is superior to a credible comparison group (i.e., one that accounts for the passage of time, increased attention, expectation of therapeutic intervention, and the psychological consequences of legitimized sick role) (30) (Mental Health: A Report of the Surgeon General, 1999). An intervention is *probably efficacious, pending replication* (i.e. the intervention has *supportive evidence of efficacy* but the results need to be replicated) if there is at least 1 RCT (or 2 or more RCTs conducted by the same investigative team) showing that the intervention is superior to a credible comparison group. An intervention has *inconclusive evidence*, if it doesn't fit into any of the two previous categories, for example, there has been only 1 RCT with negative results.

This review does not include interventions at the organizational level or systems-level collaborative care models, including IMPACT (31), PROSPECT (32), HOPE-D (33), PRISM-E (34), and RESPECT (35) as the relative effect of psychosocial interventions cannot be determined by the designs of these studies. Further, the treatments were given in combination with other depression interventions, clouding the overall impact of psychosocial interventions (36); for example, in IMPACT, patients who received PST were often also treated with antidepressant medication, and those who were not were provided with case management support and behavioral activation strategies.

During our search, we encountered RCTs of psychosocial interventions in mixed samples of participants with diagnosis of MDD and of participants with diagnosis of minor depression and/or dysthymia. These studies were not included because they did not meet the aforementioned *study design and statistical criteria*. Specifically, most of the studies did not

have ≥ 30 MDD participants per arm, did not perform intent-to-treat between treatment-groups statistical analyses in the MDD subgroup, or their randomization was not stratified by depression diagnosis (for example, 37–48).

Moderators of Treatment Effects in RCTs: To design subsequent studies that focus on personalized treatment, we need to identify moderators of treatment effects (49–50). *Moderators* are pre-treatment variables that are associated with a between treatment groups effect size (49). For instance, patients with baseline executive dysfunction may respond better to interventions that rely on compensatory cognitive strategies to improve mood than interventions that do not use these strategies, whereas patients without cognitive impairment may have comparable responses with either intervention. Initial analyses of moderators are exploratory. Descriptive, not inferential, analyses are used; the focus is on the magnitude of the treatment effect, not on p-values (49).

Predictors of Treatment Outcomes: To help identify potential moderators for future RCTs, we examined predictors of treatment outcomes in studies of psychosocial interventions for the acute treatment of LLMD. Predictors include baseline variables that have a main effect but not necessarily an interaction effect with treatment (i.e. if they had an interaction effect, they would, in fact, be moderators) or post-baseline variables that are correlated with treatment outcome. To broaden the list of predictors, we used less stringent criteria than those evaluating efficacy and moderators of treatment effects, including open-acute trials in addition to RCTs (Table 2).

RESULTS AND DISCUSSION

We identified 404 articles, 78 of which were clinical trials of psychosocial interventions in older adults and were published in English. Thirty-nine of those focused on the acute treatment of elders with diagnosis of unipolar, non-psychotic, major depression (MDD). Eight articles were excluded because they performed interim analyses or did not fully randomize their participants (51–58). Thirteen articles performed analyses on predictors of treatment outcomes (5, 59–70); these articles were included only in the analyses of predictors. The remaining eighteen RCT articles met the specified *study design criteria* and only six of those met the additional *statistical criteria* of ≥ 30 participants per arm and intent-to-treat analysis (Table 1).

In the final selection of 6 studies, there were only 4 unique samples: 1) Thompson et al., 2001 (71); 2) van Shaik et al., 2006 (72) and Bosmans et al., 2007 (73); 3) Arean et al., 2010 (74) and Alexopoulos et al., 2010 (75); and 4) Sirey et al., 2010 (76). van Shaik et al., 2006 (72) and Bosmans et al., 2007 (73) conducted analyses of the same sample on depression and cost, respectively, while Arean et al., 2010 (74) and Alexopoulos et al., 2010 (75) performed analyses of the same sample using a depression and disability outcomes respectively.

WHICH INTERVENTIONS ARE EFFICACIOUS?

This is the first important question whose answer will guide us toward efficient development of personalized approaches to psychosocial interventions. Our determination of efficacy was based on the 6 articles that met both *study design and statistical criteria*. No psychosocial interventions met the criteria of being *efficacious* for the acute treatment of late-life major depression, three psychosocial interventions were *probably efficacious, pending replication*, i.e. have *supportive evidence of efficacy, pending replication* (Problem Solving Therapy; Cognitive Behavioral Therapy; Treatment Initiation and Participation Program), and two interventions demonstrated *inconclusive* results (Interpersonal Psychotherapy; Supportive Therapy).

PSYCHOSOCIAL INTERVENTIONS WITH SUPPORTIVE EVIDENCE OF EFFICACY, PENDING REPLICATION

1. Problem Solving Therapy: PST targets depression by systematically teaching patients skills for improving their ability to deal with specific everyday problems and life crises, rather than developing generic skills. Patients identify problems, brainstorm different ways to solve their problems, create action plans, and evaluate their effectiveness in implementing the best possible solution.

Results: Only one RCT met both *study design and statistical criteria* (74, 75). Arean et al., 2010 and Alexopoulos et al., 2010 presented the study results on depression and disability outcomes respectively. The study tested PST vs. Supportive Therapy in 221 older subjects with major depression and executive dysfunction.

Depression (74): Participants in PST had significantly greater reduction of depression (HDRS) than participants in the ST condition (at week 9, Cohen's $d=0.24$; at week 12, Cohen's $d=0.39$). **Disability (75):** In an analysis that examined the efficacy of PST vs. ST on the disability outcome, participants in PST had significantly greater reduction in disability (WHODAS-II) than participants in ST by approximately 0.18 points per week.

Conclusion: Based on this RCT, PST is *probably efficacious in reducing depression and disability, pending replication*. These results are consistent with two PST studies that met the study design but not the statistical criteria (77, 78). Specifically, participants receiving PST had greater reduction in depression than those receiving reminiscence therapy or those who were waiting to receive treatment (77). Further, in a preliminary study of PST vs. ST in a sample of elders with major depression and executive dysfunction, PST participants had significant reduction in depression and in disability and higher remission rates (Hamilton Depression Rating Scale-HDRS <10) compared to ST participants (78).

2. Cognitive Therapy (CT) and Cognitive-Behavioral Therapy (CBT): Studies followed the approach of Beck et al., (1979) (79), which was modified by Emery (1981) (80) and Thompson et al., 2000 (81) for older adults. Patients were taught to monitor, evaluate and modify negative dysfunctional thoughts, distorted perceptions and beliefs, and learn to utilize cognitive techniques such as reattribution, listing pros and cons, and examining the evidence. In addition to the cognitive techniques, patients were encouraged to increase their activity scheduling.

Results: Only one RCT met both *study design and statistical criteria* (70) (Table 1). In this study, CBT + Desipramine was compared with CBT-alone and Desipramine-alone. The patients were seen twice a week for the first 4 weeks and once for the following 8–12 weeks. Desipramine was started at a low dose of 10 mg and was gradually increased depending on the patient's tolerance to side effects, following a protocol developed by NIMH Treatment of Depression Collaborative Research Program (82). The mean stable daily dose of desipramine was 90 ± 63 mg and the mean plasma level of desipramine was 123 ng/mL. In the CBT+Desipramine condition, the CBT therapist followed the same protocol as in the CBT-alone condition.

The authors performed a growth curve analysis that included missing data points and participants who discontinued treatment. The results demonstrate that patients in CBT +Desipramine group had significantly greater reduction than participants in the Desipramine-alone condition in both interviewer (Hamilton Depression Rating Scale) (Rate of change per session: Desipramine= -0.20 ; CBT+Desipramine= -0.41) and self-report depression (Beck Depression Inventory-Short Form) instruments (Rate of change per

session: Desipramine=-0.10; CBT+Desipramine=-0.44). Further, participants in the CBT-alone condition had significantly greater reduction in depression compared to Desipramine-alone condition in BDI-SF and comparable reductions in depression in HDRS.

Conclusion: Based on this RCT, CBT is a *probably efficacious psychosocial intervention, pending replication*. Additional RCTs that met the study design but not the statistical criteria have also shown that CBT participants had greater reduction in depression than those who were delayed treatment (83–84). Further, in a large primary care study of participants diagnosed with major or minor depression (88% MDD, 12% Minor), participants receiving CBT had significant greater reduction in depression than participants in treatment as usual or participants in a “talking control” condition, during which therapists showed warmth and interest but did not give any advice or promote problem solving (48).

3. Treatment Initiation and Participation Program (TIP) (76, 85): The TIP intervention is a brief, individualized intervention in primary care in conjunction with pharmacotherapy that identifies barriers to adherence in antidepressant medication treatment and utilizes cognitive behavior techniques to address these barriers and improve adherence to treatment. TIP is based on the Theory of Reasoned Actions and targets modifiable factors of adherence (86) including psychological barriers, stigma, concerns surrounding treatment, and fears of antidepressants (76, 85). TIP includes 3 inperson sessions (30 minutes each) during the first 6 weeks of pharmacotherapy and 2 short follow-up telephone sessions. The duration of intervention is 12 weeks.

Results: Only one RCT (55) met both *study design and statistical criteria* (Table 1). Participants in TIP had significantly greater reduction in depression at 12 weeks (end of intervention) than participants in the UC group. Further, TIP participants achieved higher adherence rates to antidepressant treatment than participants in the control group. Specifically, at the 12-week follow up, 82% of TIP participants were adherent (at the 80% level or above) compared to 43% of participants in the treatment as usual arm.

Conclusion: TIP is a *probably efficacious psychosocial intervention in conjunction with pharmacotherapy, pending replication*. In another study that met the study design but did not meet the sample size criterion (85) also demonstrated that TIP participants had a significant reduction in depression at 12 weeks than usual care participants.

INTERVENTIONS WITH INCONCLUSIVE EVIDENCE

1. Supportive Therapy: Supportive Therapy is based on person-centered psychotherapy and consists of 12 individual sessions. The sessions focus on facilitating expression of affect, highlighting positive and successful experiences, offering empathy, and imparting therapeutic optimism. Therapists do not utilize main therapeutic strategies found in PST, CBT, Interpersonal Psychotherapy (IPT), or dynamic therapy but they engage in empathic listening, reflection, emotional processing, and encouragement.

Results and Conclusion: Only one RCT (74–75) met both criteria. In this study, PST was more efficacious than ST in reducing depression and disability (see results above in PST). However, ST reduced depression over 12 weeks and had a significant reduction in depression in the first 6 weeks of treatment (74–75). Despite the encouraging results, ST has not yet demonstrated greater efficacy than a credible comparison group in LLMD. Future studies may concentrate on comparing the efficacy of ST with psychological or pill placebo and on identifying subgroups of patients treated with ST (using moderators analysis) with a more beneficial course of illness.

2. Interpersonal Psychotherapy (IPT): IPT focuses on complicated grief, role transition, role dispute / interpersonal conflicts and interpersonal deficits (87). The initial treatment phase includes exploration of depression symptoms and psycho-education. In later phases, problems are identified and understood in the interpersonal context. Depending on each patient's problem, treatment focuses on facilitating grieving process, encouraging and facilitating role transition, exploring interpersonal disputes, and improving interpersonal skills. In the final phase, the therapist focuses on the gains and limitations of therapy and the prevention of relapses. Depending on the study, the duration of treatment and number of sessions ranged from 16–20 weeks and 12–16 sessions respectively.

Results: One unique study met both study design and statistical criteria (72–73), and two articles were published on depression (72) and cost (73) outcomes. IPT was compared to usual care and participants were recruited through 12 primary care services in Amsterdam. The number of IPT sessions was reduced from 14 to 10 for use in primary care and the treatment was completed in 5 months. IPT was administered by 6 psychologists and 9 psychiatric nurses with more than 5 years of experience in mental health care; 13 had 2 or more years experience working with older patients.

Even though a significant higher percentage of IPT participants, compared to UC participants, did not have a depression diagnosis at 6 months (1 month after the end of treatment) (50.7% vs. 33.8%), there were no significant differences in percentages of responders (50% reduction in Montgomery Asberg Depression Rating Scale-MADRS) (IPT=27.6% vs. UC=29%) or remitters (MADRS score<10) (IPT=32.8% vs UC=32.3%) between the two groups. Further, there were no significant differences between IPT and UC at 6 months on any subscale of SF-36. In another high quality RCT of complicated grief (88NN_69) that did not meet the sample size criterion of 30 participants per arm, IPT did not show a significant main or interaction effect with NT on remission.

Conclusion: Even though research has shown that IPT is an efficacious treatment of depression in young and middle-aged adults (89) and clinical experience may suggest that IPT may reduce depression in older adults, there is no clear supportive evidence for the efficacy of IPT as an acute treatment of late-life major depression. Therefore, further research is recommended.

WHAT ARE KNOWN PREDICTORS OF TREATMENT OUTCOMES AND MODERATORS OF TREATMENT EFFECTS?—Not every depressed older adult responds to treatment equally. Therefore, specific patients may respond better to specific psychosocial interventions. To maximize the effects of our treatments, we need to first understand under what circumstances a psychosocial intervention is effective and what are the active ingredients of effective treatments. To effectively investigate personalized treatments, we need to identify moderators of treatment effects. To help identify moderators for subsequent RCTs, we also examine predictors of treatment outcomes.

Few studies of psychosocial interventions in late-life major depression have looked at predictors of treatment outcomes and moderators of treatment effects. We identified 14 studies that investigated predictors of treatment outcomes (Table 3); four of those were RCTs, nine were open acute treatment trials using pharmacotherapy and IPT and one study added a psychosocial intervention to randomized pharmacotherapy groups for the treatment of major depression with alcohol dependence (62). Three RCTs examined moderators (70, 72, 74–75). Two of these studies examined moderators of treatment effects in the same sample (74–75) but on different outcomes (depression and disability).

1. Predictors of treatment outcomes of psychosocial interventions in late-life major depression:

The most commonly examined predictors (i.e. examined by at least 2 studies) are: a) baseline depression severity (5 studies: 5, 63, 64, 66); b) age (4 studies: 6, 63, 65, 67); c) baseline anxiety level (2 studies: 64, 68); d) personality pathology (3 studies: 65, 69, 70); e) perception of illness or self-rated health (2 studies: 63, 65); f) baseline stress level (64, 69); and g) endogenous vs. non-endogenous depression (59, 64) (Table 3). **Baseline Depression Severity:** The results are inconsistent in the predicting effects of baseline depression severity to treatment outcomes. Dew et al., 1997 (64), Gildengers et al., 2005 (5), and Karp et al., 2005 (66) found that more severe depressive symptoms at baseline predicted a slower response in acute trials of IPT+NT and IPT+Paroxetine. However, Miller et al., 1996 (63) and Lenze et al., 2001 (65) showed that depression severity at baseline was not associated with response or remission status. **Age:** The results are inconclusive on the effect of age on treatment outcomes. While age did not predict worse outcomes in two studies (65, 67), older age was associated with worse response in the other two studies (5, 63). **Baseline Anxiety Level:** Lower anxiety level predicted a more rapid, sustained response in a study of open acute treatment of NT + IPT (64). Similarly, in an open trial of Paroxetine + IPT, patients with high anxiety scores at baseline had a longer median time to response than those with low anxiety scores (68). **Perception of Illness (Self-rated Health):** Worse perception of illness and lower self-rated health at baseline was associated with lack of response and greater likelihood of failure to remit (63, 65). **Personality Pathology:** Greater personality pathology as measured by the Personality Assessment Form (90) was associated with greater likelihood of failure to remit in an open acute trial of NT + IPT (65, 69). In a secondary analysis that focused on Cluster C personality disorders (70), Cluster C PD was not associated with response status but predicted longer time to response (no PD=9.86 weeks vs. Cluster C PD=14.43 weeks). **Baseline Stress:** Low stress at baseline was associated with having a relatively more rapid, sustained response (64) and shorter time to remission (69). **Endogenous Depression:** Endogenous depression, a type of major depression that tends to have a higher genetic component and is related to poor affective control, anhedonia and agitation, appears to have a negative effect on treatment outcomes. Gallagher et al (1983) (59) demonstrated, in their clinical trial comparing Behavioral Therapy, Cognitive Therapy and Brief Relational/Insight Therapy, that patients with endogenous depression had worse depression outcomes than patients who had non-endogenous depression. Similarly, endogenous depression, in an open acute trial of NT and Interpersonal Psychotherapy, was associated with partial or mixed response (64).

2. Moderators: Four articles investigated moderators of treatment outcomes in late-life major depression; three with depression as the outcome and one with disability as the outcome. Age, education, depression onset, number of depressive episodes, baseline depression and anxiety severity, social support, overall cognitive impairment as well as executive dysfunction have been studied as potential moderators.

Thompson et al (2001) (71) studied whether baseline depression severity would moderate treatment effects of CBT, Desipramine and the combination of the two treatments. The study found that in the high severity group (HDRS-17 item ≥ 19) when an interviewer-administered instrument (HDRS) was used, participants in the Combined group had -0.31 points in HDRS greater reduction in depression per session than participants in the Desipramine group. However, in the low severity group (HDRS-17 item < 19), the between treatment difference was -0.11 in HDRS points. When a self-report measure (BDI-Short Form) was administered, participants in the Combined condition had -0.48 points in BDI greater reduction in depression per session than participants in the Desipramine group in the high severity group and -0.20 BDI points in the low severity group. These results suggest that CBT + Desipramine compared to Desipramine Alone may have better depression outcomes in the high depression severity group than in the low depression severity group.

In another study, van Schaik et al (2006) (72) investigated the moderating effect of depression severity on response to Interpersonal therapy and care as usual, and found that the between group treatment effect (Interpersonal Psychotherapy vs. Usual Care) was greater in those with high depression severity at baseline (Montgomery Asberg Depression Rating Scale score ≥ 21) than those with low depression severity at baseline (Montgomery Asberg Depression Rating Scale score < 21). Specifically, in the high severity group there was an 1.1 score difference in Geriatric Depression Scale between Interpersonal Psychotherapy vs. Usual Care at 6 months whereas in the low severity group there was a -0.9 score difference in GDS between the two treatment groups. Despite a small yet potentially clinically significant effect, the results highlight that patients with high depression severity may respond better to Interpersonal Psychotherapy than patients with low depression severity.

Arean et al (2010) (74) and Alexopoulos et al (2010) (75) investigated a series of preplanned moderators in their comparison of PST to ST in older adults with comorbid major depression and executive dysfunction. The following moderators were investigated on depression and disability outcomes: baseline depression severity, age, education, gender, age of first onset, number of previous episodes, baseline severity of executive dysfunction, overall cognitive impairment, and anxiety. While none of these variables moderated depression outcomes, patients with more cognitive impairment and higher number of depression episodes had better disability outcomes when treated with Problem Solving Therapy than with Supportive Therapy. Specifically, for an increase of 1 additional depressive episode, the change in the difference between the WHODAS slopes of the PST and the ST groups was 4.15 point at 12 weeks. Similarly, when MMSE score was increased by 1 point, the change in the difference between the WHODAS slopes of the PST and the ST groups was 4.51 points.

Conclusion: The data on the predictors of treatment outcomes and moderators of treatment effects of psychosocial interventions for late-life major depression are still preliminary. It appears that increased baseline anxiety and stress level, personality pathology, endogenous depression, and reduced self-rated health are associated with worse depression outcomes. Further, baseline depression severity may moderate the effects of CBT vs. CBT plus medication or the effects of Interpersonal Psychotherapy vs. Usual Care. Finally, problem solving treatment may be a particularly good intervention in reducing disability for older adults who have mild cognitive deficits and high number of depression episodes. Clearly, more work is needed to understand other predictors and moderators.

FUTURE DIRECTIONS—Our review demonstrates that Problem Solving Therapy (PST), Cognitive Behavioral Therapy, and Treatment Initiation and Participation Program are *probably efficacious* for the acute treatment of late-life major depression. Our findings are in agreement with findings from other reviews and meta-analyses that psychosocial interventions, including Problem Solving Therapy and Cognitive Behavioral Therapy, are efficacious in the treatment of late-life depression (including diagnosable major depression, minor depression, dysthymia, or clinically significant depression) (7–9). In our review, 18 high quality articles were initially identified, yet only 6 met the statistical criteria of ≥ 30 participants per condition and intent-to-treat analyses. These 6 studies were published in the last 10 years, reflecting the recent incorporation of statistical techniques to account for missing data (for example, mixed effects model analysis), a better understanding on the limitations of small sample size pilot studies (26), and the sample size criterion that we set forth. It is also likely that smaller sample sizes seen in these studies is a function of the expense in conducting a psychotherapy trial. Most behavioral interventionists receive their funds from agencies such as NIH, and as a result only have five years to recruit participants and limited budgets.

Our review highlights the need for novel research to identify moderators of treatment effects and guide the development of personalized approaches to psychosocial treatments. The National Advisory Mental Health Council (NAMHC) report provides us with some direction as to what the focus of this research should be. One area that has been surprisingly missing from the psychotherapy literature on late-life major depression is the role that cognitive impairments play on response to psychotherapy. As many as 30% of older adults with major depression have mild cognitive impairments and many more have cognitive complaints. The most common are memory, concentration, executive dysfunction and language processing impairments, areas that have been earmarked for investigation under the NIMH Research Domain Criteria Project. These areas of function could be particularly important in determining differential treatment response in psychotherapy. Given that psychotherapies tend to rely on these cognitive processes – and some provide a compensatory framework for certain disabilities (e.g.: problem solving therapy for executive dysfunction), exploring the role that cognitive impairment plays in response to psychotherapy could prove to be paradigm shifting for the psychotherapy field overall. Other areas that deserve attention are early life stress, emotional control, and bio-markers associated with poor response to treatment.

A number of qualifiers require mention, as the samples of the efficacy studies are highly selective. Most studies of psychosocial interventions have selected overly healthy, cognitively intact, Caucasian, younger and highly educated samples. Specifically, the average age of participants in the 14 unique samples that met our study design criteria was 69.78 years old, the average number of years of education (of the studies that reported years of education) was 13.11, and the average percentage of Caucasian participants (of those studies that reported percentages) was 86%. Therefore, there has been little focus on participants older than 80 years old, ethnic minorities, and those with cognitive impairment and low education. Future research may investigate the effect of these demographic variables on treatment outcomes.

As older adults become more cognitively and physically impaired, novel psychosocial interventions for major depression may be designed to address their needs. Application of psychosocial interventions in non-traditional settings (patients' residence, assisted living facilities, nursing homes, home-care) and focus on the patient's ecosystem (including the patient, the living environment, and the caregiver) may be necessary. Despite the advances in the diagnosis and treatment of depression in non-traditional settings, most of the studies of psychosocial interventions in these settings have been conducted with older adults without major depression diagnosis or in patients with milder forms of depression (11, 45, 91, 92). Finally, as cognitive impairment and disability increases, patients may benefit from home-delivered psychosocial interventions, the involvement of an available and willing caregiver as well as from changes in their immediate living environment that may help improve their functioning. Therefore, future studies with cognitively and functionally compromised older adults with major depression may focus on the patient's ecosystem, including the patient, their living environment and their caregiver (93).

Despite the abundance of studies on dementia, the literature on psychosocial interventions for the treatment of major depression in dementia is sparse (15, 20). Most psychosocial interventions have been tested in demented patients with either milder forms of depression, a wide range of neuropsychiatric symptoms, but not depression per se, or in samples without major depression diagnosis (15, 20). A promising behavioral treatment for depression in dementia was investigated in an RCT of a mixed sample of demented elders with major and minor depression (43). The study demonstrated that a behavioral treatment of depression significantly reduces depression in this population. In another high quality study in patients suffering from Dementia of the Alzheimer's Type but without any depression diagnosis,

exercise training combined with teaching caregivers behavioral management techniques reduced depressive symptoms compared to routine usual care (94). Finally, a pilot study testing a modified version of Dr. Teri's treatment in nursing homes has shown encouraging feasibility data (45) in a small mixed sample of patients with major and minor depression.

The dearth of studies on psychosocial interventions for patients with major depression and dementia may reflect limited funding as well as diagnostic considerations of major depression in dementia (95–96). Nevertheless, major depression has detrimental consequences for demented patients and their caregivers, including increased medical morbidity, mortality, and death from suicide (97). Further, antidepressant medications have limited efficacy in this population (97–98). Therefore, future studies on psychosocial interventions for major depression in dementia may help provide relief to demented patients and their caregivers.

Our task as intervention developers and scientists is to now focus on fine tuning treatment choices by determining which treatments are effective for the different ways that LLMD presents. Cognitive impairments, physical disability, socio-economic and biological factors may all influence response to psychotherapy overall and by type of treatment. The next steps are to better study moderators and to then guide the field in the direction of matching treatments to LLMD presentation, as well as to develop novel interventions that address comorbidities we have yet to develop treatments for.

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Randomized Clinical Trials of Psychosocial Interventions for the Acute Treatment of Late-life Major Depression that Met Study Design Criteria

Table 1

Article	Comparison Groups	Total N	Mean Age	>=30 participants per Arm	Intent-to-treat Analysis	Outcomes	Summary of Results
Gallagher et al., 1982 (99)	BT vs. CT vs. BIP	30	67.77	No	No ¹	Depression	There were no significant differences between the 3 groups at post-treatment. However, there was reduction in depression in all 3 groups on HDRS, BDI, Zung Self-rating depression scale, from an average of moderate depression severity (pre-treatment) to mild depression (post-treatment).
Thompson et al., 1987 ^a (83)	BT vs. CT vs. BDT vs. DEL	91	67.07	Yes ²	No ³	Depression / Anxiety / Coping Skills	Combined treatment had significant better scores than Delayed-Treatment Control on BDI, HDRS, BSI:Depression, BSI: Anxiety, BSI: Global Severity. There were no significant differences on any outcome among 3 treatments.
Gallagher-Thompson et al., 1990 ^a (84)	BT vs. CT vs. BDT vs. DEL	91	67.07	Yes ²	No ³	Depression	There were no significant differences among 3 treatments in terms of diagnostic outcome (major depression, minor depression, not depressed based on SADS-change interview) at post-treatment.
Areán et al., 1993 (77)	PST vs. RT vs. WLC	75	66.5	No	Yes	Depression / Well being	Subjects in PST and RT had significantly less depression at posttreatment as compared with their pretreatment scores according to all three depression measures (HDRS, GDS, BDI), whereas WLC subjects displayed no significant improvement. As expected, PST and RT participants reported significantly lower depression scores at posttreatment than individuals in the WLC condition. PST participants were also significantly less depressed than RT subjects according to their post-treatment HRSD and GDS scores but not according to their posttreatment BDI scores. Finally, only PST participants showed any significant improvement in problem solving as indicated by three SPSI scales (Problem Definition and Formulation, Generation of Alternatives, and Decision Making).
Klausner et al., 1998 (100)	GFGP vs. RT	13	66.8	No	No	Depression	Both groups had significant reduction in depression from pre to post-treatment, but participants in the GFGP group had more significant Depression improvement than RT participants in HDRS and a hopelessness combined variable. The GFGP group dropped 15 points on average; these scores were indicative of remission.
Reynolds et al., 1999 (67)	IPT+NT vs. IPT+PBO vs. PBO vs. NT	80	66.13	No	Yes	Depression / Bereavement Severity	A significant positive NT effect was detected on remission vs. no remission outcome; i.e. remission: IPT+NT=69%, IPT+PBO=29%, NT=56%, PBO=45%. There was no main effect of IPT or an interaction effect of IPT by NT. However, IPT+NT vs. IPT+PBO was significantly different, which could be interpreted that IPT may interact differently with NT than with placebo.

Article	Comparison Groups	Total N	Mean Age	>=30 participants per Arm	Intent-to-treat Analysis	Outcomes	Summary of Results
Rokke et al., 2000 (101)	Self-Management Group vs. Educational Group Therapy vs. WLC	34	67.2	No	No ⁴	Depression / Pleasant Events / Self-management	COMBINED TREATMENT VS. NO TREATMENT: 56% of WLC participants had no diagnosis of depression at post-treatment vs. 89% of participants in either Self-Management Group or Educational Group. Participants in the combined treatment had significantly reduced depression scores at post-treatment than participants in the WLC condition on BDI but not on GDS or HDRS. SELF-MANAGEMENT VS. EDUCATIONAL GROUP THERAPY: No significant differences between the two groups on percentage of participants without a diagnosis of depression at post-treatment and on reduction of depression on BDI, GDS, or HDRS.
Thompson et al., 2001 (71)	CBT vs. Desipramine vs. CBT + Des	100	66.85	Yes	Yes	Depression	There was a significant reduction in depressive symptoms as measured by the HDRS in all three conditions. Further, the per-session rate of change for the Combined condition was significantly greater than for the Desipramine condition; however, the comparisons of the Combined Condition vs. CBT-alone and of CBT vs. Desipramine were not significant.
Alexopoulos et al., 2003 (78)	PST vs. ST	25	74.12	No	Yes	Depression / Disability	PST group had greater change in depression (HDRS) scores than the ST group. Further, a significantly higher percentage of PST participants remitted than of ST participants. PST led to a more rapid improvement in disability (WHODAS-II) than ST.
Sirey et al., 2005 (85)	TIP vs. TAU	52	73.2	No	Yes	Depression / Antidepressant Treatment Adherence	TIP participants showed greater improvement in depression than the Treatment As Usual Group. Further, a significantly higher percentage of TIP participants remitted than of the control group participants. Finally, more intervention patients remained in treatment than patients in the nonintervention group.
van Schaik et al., 2006 ^b (72)	IPT vs. UC	143	67.93	Yes	Yes	Depression / Physical functioning	There was a significant higher percentage of participants in IPT without a depression diagnosis at 6 months (1 month after the end of treatment) compared to participants in UC. There was no significant differences between participants in IPT vs. participants in UC in percentages of responders or remitters (MADRS <10). Finally, there was no significant difference in reduction of depression severity between the two groups at 6 months between the two groups.
Bosmans et al., 2007 ^b (73)	IPT vs. UC	143	67.93	Yes	Yes	Cost	There were not statistically significant differences in total costs between the two groups at 6 months. Further, IPT was not significantly more cost-effective than CAU at 6 months.

Article	Comparison Groups	Total N	Mean Age	>=30 participants per Arm	Intent-to-treat Analysis	Outcomes	Summary of Results
Strachowski et al., 2007 (102)	CBT vs. WLC	48	62.24	No	No	Depression / Positive Affect / Perceived Stress / Quality of Life	There was a significant reduction from pre-treatment to post-treatment in depression (HDRS and BDI) between CBT vs. WLC. Further, participants in CBT had significant improvement in positive affect and significant reduction in perceived stress, negative affect, and in overall quality of life (as measured by SF-36) than WLC participants.
Laidlaw et al., 2008 (103)	CBT vs. TAU	40	74.03	No	Yes	Depression / Worry / Quality of Life	Participants in both groups in this study benefited from treatment with significantly reduced scores on primary measures of mood (BDI, GDS, and HDRS) at end of treatment. However, there was no significant difference on depression outcomes between participants in CBT vs. TAU.
Sirey et al., 2010 (76)	TIP vs. TAU	70	76	Yes	Yes	Depression / Antidepressant Treatment Adherence	TIP participants had higher rates of adherence than TAU participants at 12 weeks (end of intervention); specifically, 82% of TIP participants were adherent more than 80% of the time compared to 43% of participants in TAU. Further, participants in TIP had a greater reduction of depressive symptoms than participants in TAU at the end of intervention.
Areán et al., 2010 ^c (74)	PST vs. ST	221	73	Yes	Yes	Depression	Both PST and ST were associated with reduction of depression (HDRS) over 12 weeks. However, participants in PST had greater reduction of depression (HDRS) than participants in the ST condition. There was no significant difference in response or remission rates between PST vs. ST at 3 and 6 weeks but there were significantly higher response and remission rates between the two groups at 9 and 12 weeks.
Alexopoulos et al., 2010 ^c (75)	PST vs. ST	221	79.41	Yes	Yes	Disability	PST participants had significantly greater reduction in disability (total WHODAS scores) over 12 weeks than ST participants.
Kiosses et al., 2010 (104)	PATH vs. ST	30	79.41	No	Yes	Depression / Disability	Participants in both PATH and ST had reduction of depression over 12 weeks. However, participants in PATH had significantly greater reduction in depression (HDRS) and disability (Sheehan Disability Scale) over 12 weeks than ST participants. Both PATH and ST participants had comparable high rates of treatment satisfaction.

^a These studies used the same sample;

^b These studies used the same sample;

^c These studies used the same sample;

^d Eight participants dropped out before the end of the 3rd week of treatment and were replaced; as a result, they were not included in the analysis.

- ² In the first part of the study, there were four conditions: BT (N=25) vs. CT (N=27) vs. BDT (N=24) vs. Delayed Treatment Controls (N=19). However, in the second part of the study, the delayed controls were randomized to treatment and the final N was 91, with BT=30, CT=31, BDT=30.
 - ³ Eighteen patients who dropped out were not included in the analysis.
 - ⁴ 6 dropped out prematurely, 3 from the self-management condition, 1 from education control and 2 from the waiting list. None of these participants were available for posttest assessment.
- BDT: Brief Dynamic Therapy; BDI: Beck Depression Inventory; BIP: Brief Relational/Insight Psychotherapy; BT: Behavior Therapy; CT: Cognitive Therapy; CBT: Cognitive Behavioral Therapy; DEL: Delayed Treatment Condition; DBT: Dialectical Behavior Therapy; GDS: Geriatric Depression Scale; GFGP: Goal-focused Group Psychotherapy; HDRS: Hamilton Depression Rating Scale; IPT: Interpersonal Psychotherapy; MADRS: Montgomery Asberg Depression Scale; MED: SSRI, Tricyclic, Bupropion or Venlafaxine; NT: Nortriptyline; PBO: Placebo; PBOSUP: Placebo Support Group; PATH: Problem Adaptation Therapy (PATH); PST: Problem Solving Therapy; RT: Reminiscence Therapy; ST: Supportive Therapy; TAU: Treatment as Usual; TIP: Treatment Initiation and Participation Program; UC: Usual Care; WHODAS: World Health Organization Disability Assessment Schedule; WLC: Waiting-List Condition

Table 2

Predictors of Treatment Outcomes in Clinical Trials of Psychosocial Interventions for the Acute Treatment of Late-life Major Depression.

Article	Comparison Groups	RCT	Predictors Examined	Results
Gallagher et al., 1983 (59)	BT vs. CT vs. BIP	Yes	Endogenous vs. Non-endogenous Depression at Start of Therapy	Participants with non-endogenous depression had significantly lower depression scores at the end of treatment compared to participants with endogenous depression on two out of three depression instruments (HDRS and BDI but not Zung SDS). The groups had comparable pre-treatment depression scores. Similarly, a significantly higher percentage of participants with non-endogenous depression were responders at the end of treatment compared to participants with endogenous depression based on BDI ≤ 10 .
Marmar et al., 1989 (60)	BT vs. CT vs. BDT	Yes *	Patients' and Therapists' Ratings of Treatment Alliance at 5th session	Ratings of treatment alliance completed by therapists at 5th session were not significantly correlated with treatment outcome. However, ratings in a single domain of treatment alliance, Patient Commitment, when completed by patients at 5th session were significantly correlated with treatment outcomes in the whole sample and in those patients in the CT arm.
Gaston et al., 1989 (61)	BT vs. CT vs. BDT	Yes *	Patients' expectations of three change processes (Insight and Support, Behavioral and Cognitive Changes, and Medication and Environmental Changes)	Levels of patient expectations of change processes were not significantly different among BT vs. CT vs. BDT. Patient expectations of change processes were not related to depression outcome (HDRS). However, greater expectation of gaining help through behavioral and cognitive changes was associated with less depressive symptoms at termination in CT; this association was not present in BT or BDT.
Karp et al., 1993 (69)	Open acute treatment of NT + IPT	No	Sociodemographic and clinical variables, including age, presence of a stress-provoking agent, personality pathology, social support.	Presence of a stress-provoking agent, eccentric cluster personality features (i.e., paranoid, schizoid, and schizotypal) and earlier age at first episode were associated with prolonged time to remission. Two of the four variables, presence of a stress-provoking agent and perception of diminished social support, were also significant in the final model.
Miller et al., 1996 (63)	Open acute treatment of NT + IPT	No	Perception of illness, age, baseline depression severity and medical burden.	Age and baseline perception of illness, but not baseline medical burden or depression severity, predicted response in 75% of the participants.
Dew et al., 1997 (64)	Open acute treatment of NT + IPT	No	Baseline chronic stress, depression severity, anxiety level, social support, likelihood a life stressor precipitated current episode, age at first lifetime episode, subjective sleep assessment, percentage of REM sleep, REM activity.	Baseline low chronic stress, low likelihood that a life stressor precipitated current episode, older age at first lifetime episode, less severe depressive symptoms, lower anxiety level, less subjective sleep impairment, lower percentage of REM sleep, and less REM activity were the most important predictors of having a relatively more rapid, sustained response. In contrast, poor social support, high likelihood that a major life stressor precipitated current episode, endogenous depression, and long sleep latency were associated with partial or mixed response.
Reynolds et al., 1999 (67)	Open acute treatment of NT + IPT	No	Two age groups (60–69 vs. 70+ year old)	The two age groups (below 70 and 70+) did not differ in absolute remission rates and in time-to-remission.
Lenze et al., 2001 (65)	Open acute treatment of NT + IPT	No	Age, gender, education, baseline depression severity, social adjustment, personality pathology, social adjustment, and disability.	Lower self-rated health (perception of illness), greater personality pathology, and greater IADL disability were associated with greater likelihood of failure to remit in univariate analysis; however, only lower self-rated health was associated with greater likelihood of failure to remit in the multivariate model. Participants who recovered had significant improvement in depression, IADL disability, social adjustment, and self-rated health (perception of illness).
Gildengers et al., 2005 (5)	Participants from open acute	No	Baseline depression severity, self-esteem, illness duration, age.	Greater baseline depression severity was a significant risk factor for slower response in NT + IPT and in PX + IPT samples. Higher self-esteem was significantly associated

Article	Comparison Groups	RCT	Predictors Examined	Results
	treatments with NT + IPT or Paroxetine + IPT			with more rapid response in NT + IPT while longer duration of illness was associated with a slower response trajectory in PX + IPT. Similarly, greater baseline depression severity was a significant risk factor for nonresponse in PX + IPT, but not in NT + IPT while older age was associated with nonresponse in the NT + IPT sample.
Oslin et al., 2005 (62)	Naltrexone + Sertraline + Psychosocial Intervention vs. Sertraline + Psychosocial Intervention	No	Heavy drinking, complete abstinence	Relapse to heavy drinking was associated with a reduction in treatment response as measured by remission of depression or by absolute improvement in symptoms. Complete abstinence was not associated with improvement in depression. Similar findings were found when considering the percentage of days of heavy drinking. More frequent bouts of heavy drinking during the trial were associated with lower rates of improvement in depression and reduction in Ham-D scores.
Karp et al., 2005 (66)	Open acute treatment of Paroxetine + IPT	No	Baseline depression severity, suicide ideation, body pain.	Baseline severity of depressive symptoms, Ham-D Suicide Probe, and pain were significantly lower in the subjects who responded vs. in those who did not. Cox proportional hazards model analysis revealed a significant relationship between baseline BPI scores and time-to-response that became non-significant after covarying for baseline depression severity.
Morse et al., 2005 (70)	Open acute treatment of NT + IPT	No	Cluster C Personality Disorder (PD)	Cluster C PD was not associated with residual depressive symptom status or responder status at the end of acute treatment; however, Cluster C PD predicted longer to response (median time to response: no PD=9.86 weeks; Cluster C PD=14.43 weeks). Finally, Cluster C PD was not associated with worsening of functioning; in both groups, functioning improved at the same rate during acute treatment.
Andreescu et al., 2007 (68)	Open acute treatment of Paroxetine + IPT	No	Baseline anxiety level.	A statistically lower percentage of patients with scores above the median in the anxiety scale of BSI achieved response compared to the percentage of patients with scores below the median who achieved response (52% vs. 75% respectively). Patients with higher BSI scores had a significantly longer median time to response than those with lower BSI scores (11 vs. 6.7 weeks).

BDI: Beck Depression Inventory; BIP: Brief Relational/Insight Psychotherapy; BT: Behavior Therapy; CT: Cognitive Therapy; CBT: Cognitive Behavioral Therapy; GDS: Geriatric Depression Scale; HDRS: Hamilton Depression Rating Scale; IPT: Interpersonal Psychotherapy; PST: Problem Solving Therapy; RT: Reminiscence Therapy; ST: Supportive Therapy; UC: Usual Care; WLC: Waiting-List Condition.

^aThese two articles performed analyses on the same sample but with different outcome.

* Study was conducted on a subset of participants of the original RCT (Thompson et al., 1997; Gallagher-Thompson et al., 1990)

Table 3

Moderators of Treatment Effects in Randomized Clinical Trials of Psychosocial Interventions for the Acute Treatment of Late-life Major Depression.

Article	Comparison Groups	Moderators - Examined	Moderators - Results
Thompson et al., 2001 (71)	CBT vs. Desipramine vs. CBT + Des	Baseline Depression Severity; High-Severity Group (HDRS>18) and Low-Severity Group (HDRS≤18)	For BDI-Short Form: BDI improvement per session in CBT+Desipramine participants between High vs. Low Severity Groups was significant (Low Severity= -0.29 vs. High Severity =0.58). However, BDI improvement per session in the other two treatment conditions was not significantly different between the High vs. Low Initial Severity Groups.
van Schaik et al., 2006. (72)	IPT vs. UC	Baseline Depression Severity: MADRS ≥21 (High) vs. MADRS <21 (Low)	In the subgroup of participants with high baseline depression severity, a significantly higher percentage of participants in the IPT group vs. in UC had no diagnoses of depression (or lower depression score (measured by GDS-15) at 6 months. However, in the low baseline severity group, there was no significant difference in the percentage of participants in the IPT group vs. in UC with no diagnoses of depression or lower GDS-15 scores.
Areán et al., 2010 ^a (74)	PST vs. ST	Examined moderators of treatment effects on depression. Baseline variables: Age, Education (years), Depression Severity, Age at depression onset (years), Total number depressive episodes, Overall Cognitive Impairment, Executive Dysfunction, Personality Characteristics, Disability, Generalized Anxiety Disorder.	None of these variables moderated the efficacy of treatment on depression.
Alexopoulos et al., 2010 ^a (75)	PST vs. ST	Examined moderators of treatment effects on disability. Baseline variables: Age, Education (years), Depression Severity, Age at depression onset (years), Total number depressive episodes, Overall Cognitive Impairment, Executive Dysfunction, Personality Characteristics, Disability, Generalized Anxiety Disorder.	PST was associated with greater reduction of disability than ST in patients with higher number of depressive episodes and greater cognitive impairment (i.e., lower MMSE scores). Specifically, for an increase of 1 additional depressive episode, the change in the difference between the WHODAS slopes of the PST and the ST groups was 4.15 points. When MMSE score was increased by 1 point, the change in the difference between the WHODAS slopes of the PST and the ST groups was 4.51 points.

CBT: Cognitive Behavioral Therapy; HDRS: Hamilton Depression Rating Scale; IPT: Interpersonal Psychotherapy; MMSE: Mini Mental State Exam; PST: Problem Solving Therapy; ST: Supportive Therapy; UC: Usual Care; WHODAS: World Health Organization Disability Assessment Schedule

^aThese two articles performed analyses on the same sample but with different outcomes: Areán et al., 2010 - Outcome=Depression; Alexopoulos et al., 2010 - Outcome=Disability.