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Late-life Depression: Evidence-based Treatment and Promising New Directions for Research and Clinical Practice

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OVERVIEW

Depression results in more years lived with disability than any other disease, and ranks fourth in terms of disability-adjusted life years.[1–3] Projections are that, by 2020, depression will be second only to heart disease in its contribution to the global burden of disease (measured by disability-adjusted life years).[4] As the population ages, successive cohorts of older adults will experience depressive disorders.[4] Late-life depression (LLD) carries additional risk for suicide, medical comorbidity, disability, and family caregiving burden.[5–7] Although treatment is effective in reducing symptoms, it is less successful in achieving and maintaining remission and in averting years lived with disability. Although response and remission rates to pharmacotherapy and electroconvulsive therapy (ECT) are comparable with those in midlife depression, relapse rates are higher,[8] underscoring the challenge not only to achieve but also to maintain wellness.

This article reviews the evidence base for LLD treatment options and provides a more in-depth analysis of treatment options for difficult-to-treat LLD variants (eg, psychotic depression, vascular depression). Treatment algorithms are also reviewed based on predictors of response and novel treatment options that represent promising leads.

Standard Treatment

Pharmacotherapy—Approximately two-thirds of patients presenting with severe forms of depression respond to antidepressant treatment. However, older, frail people are particularly vulnerable to antidepressant side effects, especially cardiovascular and anticholinergic side effects, and this can compromise compliance and effectiveness of treatment.[9]

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Acute Treatment

A recent meta-analysis of acute pharmacological trials revealed a paucity of placebo-controlled trials in older depressed populations.[10] Using a 50% reduction in the Hamilton Rating Scale for Depression (HRSD) as the primary outcome measure, the meta-analysis reported an overall number needed to treat (NNT) of 8 (95% confidence interval [CI] 5,11) when all antidepressant classes were collapsed together.[10] The analysis of each class was similar: for tricyclic antidepressants (TCAs) the NNT was 5 (95% CI 3,9) and for selective serotonin reuptake inhibitors (SSRIs) the NNT was 8 (95% CI 5,11). Because the confidence intervals between TCAs and SSRIs overlap substantially, these data do not support that one drug class is more effective than another.[10] A limitation of the studies examined in this meta-analysis is that they were efficacy trials, excluding subjects with comorbid psychiatric illnesses, medical comorbidity and poor treatment response history, thus limiting generalizability.[10] Moreover, the largest trials conducted so far showed a large placebo response rate and a significant number of subjects who do not respond or who have residual depressive symptoms.[10]

In a large (N = 728) trial, Nelson and colleagues[11] used the HRSD to determine the symptoms that showed the greatest improvement during treatment: depressed mood (effect size [ES] 0.93), decreased interest and activity (ES 0.86), psychic anxiety (ES 0.65), guilt (ES 0.63), suicidal ideation/behavior (ES 0.6). Consequently, the investigators compared the results with those obtained using 5 other scales (Montgomery Asberg Depression Rating Scale, the Keller Brief Depression Rating Scale, Yale Depression Inventory, Quick Inventory of Depressive Symptoms, Inventory of Depressive Symptoms) and reported that there is considerable agreement among the scales with regard to symptoms sensitive to change during treatment of LLD.[11]

LLD is also more varied in its clinical presentations than its midlife equivalent. Thus, instruments currently used to define depression might not capture the entire spectrum or phenotype of depressive disorders in the elderly. Moreover, instruments such as HRSD or Montgomery Asberg Depression Rating Scale are difficult to use on a regular base in the real-life environment of the currently overcrowded outpatient clinics. Self-report measures, such as PHQ9, provide a more practical, easy-to-use tool for measure-based care, and fit in well with the strategies of depression care management.[10]

An effectiveness trial of older depressed outpatients reported a post hoc analysis for participants treated with citalopram in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) analyzing the correlation between age of onset of the first MD episode and clinical outcome.[12] Remission rates (defined by a 16-item Quick Inventory of Depressive Symptomatology-Self-rated) were not statistically different between earlier onset (age of onset <55 years; 30.8%) and late onset (31.9%).[12]

A 2006 Cochrane Review on the use of antidepressants in the elderly examined the efficacy of antidepressant classes, compared the withdrawal rates associated with each class, and described the side effect profile of antidepressants for treating depression in patients age 55 years and older.[9] The review did not find any differences in efficacy between classes of antidepressants, although it reported that TCAs are associated with a higher withdrawal

rate because of side effect experiences (Table 1).[9] The small number of studies restricted the validity of subgroup analysis on different populations (outpatient/inpatients/community volunteers/nursing home residents).[9] Because few trials used standardized instruments to report side effects, the Cochrane Review used an analysis of withdrawal rates and described the ratios of the number of side effects experienced by patients treated with each antidepressant class. Thus, TSA recipients experienced more gastrointestinal side effects (4.6 side effects experienced by 10 TCA recipients compared with 2.9/10 SSRI recipients) and more neuropsychiatric side effects (4.1 side effects experienced by 10 TCA recipients compared with 2.3/10 SSRI recipients). However, nausea and vomiting were experienced by a greater percentage of SSRI recipients.[9] A STAR*D report on melancholiform depression in midlife reported that the presence of melancholic features was associated with significantly reduced remission rates to SSRI (8.4% compared with 24.1% in nonmelancholiform depression).[13]

Overall, these studies underscore the similar incomplete response to antidepressant treatment across the life cycle and highlight the challenge to develop novel, more efficacious treatment strategies, especially for patients who do not respond fully to first-line treatments. The goal of acute, or short-term, treatment is full remission of symptoms. The goal of longer-term treatment is prevention of recurrence. Getting well is important but not enough. It is staying well that counts.

Maintenance Treatment

There is limited consensus about the length of long-term maintenance pharmacotherapy after a first episode of depression, most experts recommending 6 to 12 months of pharmacotherapy after a first episode of depression in old age.[14] Recurrence rates in LLD range from 50% to 90% in a period of 2 to 3 years.[15] Thus, the goal of the treatment is not only acute recovery but also prevention of recurrence.[16] There are few controlled studies on the efficacy of maintenance antidepressant medication. Maintenance nortriptyline (plasma steady-state level 80–120 ng/mL), monthly interpersonal therapy (IPT), and the combination of the 2 were superior to placebo in preventing recurrence for 3 years among patients with LLD with a history of multiple episodes.[17] Citalopram (dose 20–40 mg/d)[18] but not sertraline (50–100 mg/d)[19] have differed from placebo in 2 randomized trials following subjects for 48 and 100 weeks respectively. The most recent study to date to test the efficacy of an SSRI in maintenance treatment of LLD tested the efficacy of 2-year maintenance treatment with paroxetine and monthly interpersonal therapy.[16] Major depression recurred in 35% of the patients receiving paroxetine and psychotherapy, 37% of those receiving paroxetine and clinical management sessions (30-minute visits with no specific therapy, questions about symptoms and possible side effects), 68% of those receiving placebo and psychotherapy, and 58% of those receiving placebo and clinical management sessions.[16] The relative risk of recurrence among patients receiving placebo was 2.4 times that among those receiving paroxetine (dose 10–40 mg/d).[16] Moreover, patients treated with paroxetine for 2 years were less likely to have recurrent depression, whereas maintenance psychotherapy did not prevent recurrences.[16] Patients in their first lifetime episodes also benefited from maintenance treatment of 2 years, thus not supporting the conventional wisdom and practice

of limiting continuation treatment to 6 to 12 months following remission from acute treatment.[16]

Another important and clinically relevant aspect of maintenance treatments is that the NNT is around 4, in contrast with an NNT of 7 to 8 in acute treatment. In comparison, 4 large trials of statins found that the number of patients needed to be treated with statins for 5 years to prevent another myocardial infarction was 21,[16] indicating a larger clinical effect size for maintenance antidepressant pharmacotherapy.

Psychotherapy—Given the propensity to multiple side effects noticed in the elderly, psychotherapy may represent a safer alternative. Most guidelines advocate the additional benefit of supporting antidepressant medication with psychosocial interventions.[6,17,20] An expert-consensus guideline from 2001 considered cognitive behavioral therapy (CBT), problem-solving therapy (PST), IPT, and supportive therapy as first-line psychosocial interventions, whereas psychodynamic therapy received a more controversial rating (26% of the experts rated this as first line and 36% as third line).[14] Overall, the expert consensus recommended psychotherapy as an adjunctive treatment to medication, except for mild depression or dysthymia, for which psychotherapy alone was considered an alternate initial treatment strategy.[14] The more commonly prescribed psycho-therapies are developed from cognitive therapy, which focuses on dysfunctional beliefs; they include CBT, PST, and behavioral activation. Numerous descriptive studies have examined the technical issues in adapting these therapies to aging populations: emphasizing behavioral techniques, repeating information, a slower pace, and using different sensory modalities.[21] Thus, given the executive dysfunctions described in LLD,[22] several experts advocated for the use of PST[23,24] that uses behavioral activation and explicitly trains patients to select and solve daily problems as a way of increasing self-efficacy and overcoming the feelings of helplessness at the core of depression.

However, there is little evidence based on randomized controlled trials that specifically examines the efficacy of various types of psychotherapy in older people.

A Cochrane Review from 2007 identified 9 trials of CBT and psychodynamic therapy, 7 of these providing comparison data between CBT and controls.[20] CBT was more effective than waiting list controls, whereas there was no difference in treatment effect between CBT and psychodynamic therapy. However, the superiority CBT to waiting list was maintained only when assessed via the HRSD; it disappeared when using the Geriatric Depression Scale (GDS).[20] All the trials analyzed had small sample sizes, the inclusion criteria allowed for both major depression and dysthymia, included both clinical populations as well as community volunteers,[25] with duration varying from 4 to 24 weeks.[20] The investigators concluded that, although CBT-derived therapies seem to be superior to waiting list control, the small size of the meta-analysis, the high dropout rates, and the heterogeneity of the study populations and the interventions limited the ability to generalize these findings to clinical populations.[20]

One more recent randomized, controlled trial reported that in 4 months, CBT was more effective than treatment as usual or talking control (supportive therapy) for late-life

depressed subjects (total N = 204).[26] Another randomized, controlled trial showed that, in a period of 12 weeks, PST was superior to supportive therapy in older adults with major depression and executive dysfunction.[27] Integrating the results of 89 controlled studies of LLD acute treatment, a recent meta-analysis[28] reported that both pharmacotherapy and psychotherapy render comparable, moderate-to-large effect sizes (Cohen d 0.62–0.69 for pharmacotherapy studies and 0.83–1.09 for psychotherapy studies).

ECT

Older depressed patients are often frailer and particularly prone to the side effects of antidepressants. ECT has been established as particularly effective in LLD.[29] Although it is still controversial, ECT seems to be a safe treatment even in elderly with comorbid cardiovascular illness, dementia, or Parkinson disease.[30]

From the various randomized controlled trials of ECT for elderly people (>60 years old), only 4 trials were eligible for inclusion in the Cochrane meta-analysis, 1 comparing the efficacy of real ECT versus simulated ECT, 2 comparing the efficacy of unilateral versus bilateral ECT, and the other comparing the efficacy of weekly ECT with three times weekly ECT. However, the various methodological problems did not allow the investigators to perform a quantitative comparative analysis of these studies.[31] The investigators concluded that neither the efficacy of unilateral compared with bilateral ECT, nor of the 3-week ECT compared with weekly ECT, has been convincingly proved.[31] Moreover, studies that establish the long-term effects of ECT or those comparing the safety and efficacy of ECT with antidepressants in subpopulations such as elderly depressed with dementia or vascular disease are still needed.[31]

Post-ECT maintenance treatment with pharmacotherapy are discussed later.

Difficult-to-treat LLD

In general, the pharmacological treatment of LLD is only partially successful, with about 50% of patients improving with antidepressant monotherapy to the point of full response or remission. Many factors predict a difficult-to-treat depression, including clinical profile (comorbid anxiety, psychotic symptoms, poor sleep, low self-esteem), high medical burden, coexisting cognitive impairment.[32] Partial response poses the risk of chronic relapsing depression, nonadherence to other treatments for coexisting medical disorders, family caregiver burden, and suicide.

Treatment-resistant Depression

Treatment-resistant depression reportedly affects up to one-third of older depressed patients.[33] Before labeling an episode of depression as treatment resistant, it is important to ensure that the diagnosis is correct and that the patient has received an adequate dose of treatment, for an appropriate length of time, to assess the presence of comorbid physical and psychiatric conditions.[34] Pharmacological options of treatment-resistant depression can be grouped in 2 categories: switching or combining. In the first case, treatment is switched within or between classes of antidepressants and thus avoids polypharmacy and potential increased side effects and medication costs.[35] Combination strategies have the advantage

of building on achieved improvements and are recommended when partial response has already been obtained. The most frequently used augmenting agents are lithium, atypical antipsychotics, and thyroid hormones. A sequential treatment protocol compared augmentation with lithium, switching to monoamine oxidase inhibitors (MAOI) or to ECT in elderly with partial acute response to either venlafaxine or nortriptyline.[36] Augmentation with lithium was the best treatment option in this group for both efficacy and tolerability.[36] So far, the combination of antidepressants and atypical antipsychotics (aripiprazole and olanzapine) are the only approved augmenting agents for treatment-resistant depression. A recent pilot study in older adults using aripiprazole augmentation reported that 50% of the 24 incomplete responders to prior sequential treatment with SSRI and serotonin-norepinephrine reuptake inhibitor pharmacotherapy remitted in 12 weeks with the addition of aripiprazole (mean daily dose 10 mg) and remission was sustained during 6 months of continuation treatment.[37]

Several experimental, less well studied alternatives use central nervous system stimulants such as methylphenidate, modafinil, ω-3 fatty acids, lamotrigine, topiramate, herbal supplements, or β-blockers.[38–40]

Although there is no equivalent in the elderly of the STAR*D trial in midlife adults, Dew and colleagues[41] reported a cumulative response rate of more than 80% to successive augmentation strategies, a rate similar to that reported in the STAR*D trials.

Therefore, if patients stay the course in depression care management with evidence-based pharmacotherapy, most eventually reach full response or remission. Eliciting treatment adherence is an important part of depression care management and usually involves working with family care givers in building a therapeutic alliance.[42]

Anxious Depression

Comorbid anxiety is common in late-life depression, having a prevalence of up to 65% in clinical samples.[43,44] Several studies reported that greater severity of anxiety is associated with increased risk of withdrawal from treatment, decreased response to acute antidepressant treatment, and a longer time to both response and remission.[45] In a controlled, randomized trial, we reported that high pretreatment levels of anxiety symptoms increased not only the risk of nonresponse in acute treatment but also the risk of recurrence of depression in the first 2 years after response to antidepressant treatment.[45] Also, persistent severe symptoms of anxiety after 6 weeks of treatment were associated with longer time and lower rates of remission of LLD.[46] Among anxiety symptoms, worry more than panic predicted longer time to response and earlier recurrence in subjects with LLD treated with paroxetine (Fig. 1).[47]

Psychotic Depression

High rates of major depressive disorder (MDD) with psychotic features (as high as 45%) have been reported in elderly inpatients with depression.[48,49] Psychotic depression is associated with poorer short-term outcome, longer time to recovery, greater disability, and greater mortality than MDD without psychosis.[50] There have been only 2 randomized controlled pharmacotherapy trials of psychotic depression in older people. The first

examined the efficacy of an antidepressant alone (nortriptyline, target plasma level 100 ng/mL) versus a combination of antidepressant and antipsychotic (notriptyline plus placebo/perphenazine, mean does 18.9 mg/d).[51] The categorical response was mediocre with both the antidepressant alone and with the combination (44% and 50% respectively), the investigators hypothesizing that the low response rate might have been caused by the heterogeneity of pathogenesis of psychotic depression in older patients, some of whom might have had incipient dementia.[51] The higher frailty of older patients often leads to the use of ECT early in the course of the treatment.[52] The second controlled trial examined for 12 weeks the efficacy of olanzapine (dose 5–20 mg/d) plus placebo or a combination of olanzapine and sertraline (50–150 mg/d) in patients with psychotic depression, and reported the results in the subgroup (more than 60 years old).[53] The combination of olanzapine plus sertraline was associated with a greater remission rate than olanzapine monotherapy (41.9% vs 23.9%, $\chi^2 = 9.53$, $P = .02$).[53]

Although practice guidelines recommend the use of an antidepressant and an antipsychotic for the treatment of psychotic depression, an analysis regarding the use of pharmacotherapy in psychotic depression revealed that, with usual care, only 5% of subjects received an adequate dose of an antidepressant and a high dose of an antipsychotic.[54] The intensity of pharmacotherapy in the combination trials was significantly associated only with the duration of current depressive episode. Most subjects (84%) received no antipsychotic or, at best, subtherapeutic doses of antipsychotics, and only about half of them (48%) received therapeutic doses of antidepressants.[54] The high proportions of patients who did not receive antipsychotics or received low doses of antipsychotics may be to the result of a lack of recognition of psychotic features.[54]

ECT has been reported to show a response rate of 87% in a mixed sample of psychotic and nonpsychotic depressed subjects[55] but there is a rapid increase in depressive symptoms after ECT.[55] However, pharmacotherapy may be more practical in community settings. Post-ECT maintenance treatment seems to be more effective when Li is combined with an antidepressant than when the antidepressant (nortriptyline) is used alone (39% relapse rate for the combination versus 60% relapse rate for antidepressant monotherapy).[55]

Vascular Depression

The vascular depression hypothesis was formulated in 1997 and postulates that cerebrovascular disease can predispose, precipitate, or perpetuate a depressive syndrome in older adults.[55] Depressed older adults with subcortical ischemic lesions often have a distinct clinical presentation with motor retardation, apathy, disability, increased risk of dementia, and a low familial load of depression.[55] Most,[56–58] but not all,[59] studies documented poorer response to antidepressants for patients with depression and subcortical vascular lesions. SSRIs have so far been of limited efficacy in depressed patients with subcortical vascular lesions. Some experts recommended the use of dopamine-acting agents (especially in depressed subjects with frontostriatal impairment) or psychotropics with cathecholaminergic activity that might promote recovery following ischemic events.[60] Two studies examined the advantages of using adjuvant calcium channel blockers, concluding that the augmentation

of fluoxetine treatment with nimodipine leads to better treatment results and lower rates of recurrence at 8 months.[61,62]

Depression in the Context of Cognitive Impairment

Cognitive impairment in LLD is a core feature of the illness, contributing to disability and impaired quality of life. In a recent randomized controlled trial, the investigators tested the efficacy of added donepezil to antidepressant treatment in improving cognitive performance and reducing recurrences of depression in 2 years of maintenance treatment.[63] The overall response rate to open escitalopram (followed by duloxetine and duloxetine plus aripiprazole as needed) was about 65%. During double-blind, placebo-controlled maintenance treatment for 2 years (with adjunctive donepezil or placebo), patients randomly assigned to donepezil had small improvement in cognitive function but substantially greater rates of recurrent major depressive episodes, compared with placebo. In the subgroup of patients with mild cognitive impairment (MCI) at the start of maintenance treatment (n = 57), 3 of 30 patients on donepezil (10%) converted to dementia within 2 years, versus 9 of 27 (33%) on placebo (Fisher exact $P = .05$). The investigators concluded that augmentation of maintenance pharmacotherapy with cholinesterase inhibitors in older adults with depression depends on a careful weighing of benefits and risks, especially in those with MCI. There seems to be no benefit in patients without MCI.[63]

Major depression affects about 25% of patients with Alzheimer disease (AD) and it is a major cause of disability, being associated with increased impairment in the quality of life and activities in daily life (ADLs), greater caregiver burden, increased physical aggression, and increased risk of suicide.[64] Various studies have investigated the treatment response in depression comorbid with cognitive impairment but most included subjects with major depression but also with depressive symptoms, or subjects with various grades of cognitive impairment. Few studies focused on patients with MDD and AD. Moclobemid, citalopram, and clomipramine were found to be superior to placebo in the short-term treatment of depression in AD.[65–67] A 12-week randomized controlled trial showed that sertraline (mean dose 95 mg/d) was superior to placebo (effect size 0.85) in treating MDD in patients with AD.[64] Sertraline-treated patients also had a trend toward less ADL decline, although there was no benefit to cognition as assessed by the Mini Mental State Examination at 12 weeks.[64] However, a follow-up report examining the week 24 outcome of patients who participated in the trial found no between-groups differences in depression response or remission rates or secondary outcomes (such as ADL decline), concluding that sertraline may not be beneficial for long-term treatment of depression in AD.[68] The association between damage to the locus coeruleus and depression in AD suggests a better efficacy of noradrenergic than serotoninergic antidepressants. We only found 1 study comparing the efficacy of citalopram and mianserin in elderly depressed subjects with dementia.[69] On balance, the evidence supporting the efficacy of antidepressant pharmacotherapy for depression in AD is mixed and inconclusive.

Bipolar Depression

Manic and bipolar depressed patients represent 5% to 15% of patients presenting for acute treatment at geriatric psychiatry services.[70] There are no systematic studies of the

treatment of bipolar depression in the elderly,[70] and clinicians usually rely on data from mixed-age studies, case reports, or uncontrolled trials.[71] Various strategies have been proposed, including combinations of paroxetine and lithium[72] and the preferred use of SSRIs and bupropion rather than tricyclics.[70] Optimal mood-stabilizer dosing for lithium in bipolar elderly patients has not been assessed, and its tolerability in the elderly is a particular concern (increased cognitive impairment, neurological side effects, delirium, sick sinus syndrome, hypothyroidism, polyuria, edema).[73] Experts recommend lower doses than for mixed-age patients (0.5–0.8 mEq/L), but lithium toxicity has been reported in the elderly even at moderate concentrations (0.5–0.8 mEq/L).[70] Other recommendations include combination of lithium and an SSRI, the use of lamotrigine or other anticonvulsants, or the addition of an atypical antipsychotic.[70] ECT should also be considered in patients with bipolar depression or rapid cycling symptoms refractory to pharmacotherapy, in suicidal patients, or those with inadequate food and fluid intake.[70]

A retrospective analysis of the efficacy of lithium (mean dose 750 mg/d) and lamotrigine (mean dose 240 mg/d) in the maintenance treatment geriatric bipolar disorder reported that lamotrigine but not lithium maintenance therapy significantly delayed time to intervention for a depressive episode.[71]

At this time there are no studies exploring the impact of cognitive impairment or of comorbid medical conditions on acute/long-term treatment of bipolar depression in the elderly.

Predictors of Treatment Response: Use of Treatment Decision-making Trees

Successful antidepressant treatment is one of the most effective ways to reduce disability, prevent morbidity, and improve quality of life in older depressed patients. However, LLD is often resistant to treatment and may exhibit a slower resolution of symptoms than midlife depression.[74] The identification of predictors of treatment response would allow the clinicians to modify treatment options earlier in the course of the treatment.

Several studies explored the biological, clinical, and psychosocial predictors of treatment response in LLD (Table 2).

However, it may be difficult for clinicians to integrate the various predictors reported in the literature into a practical treatment strategy. In an analysis that pooled data from the acute treatment phase of 3 National Institute of Mental Health–funded treatment studies, we attempted to integrate and develop a hierarchy of clinical predictors of treatment response.[75] Using signal detection theory,[76] we built 2 different models by modulating the sensitivity threshold for each predictor of treatment response to obtain hierarchies of risk correlates with different patients' characteristics.

Thus, for patients requiring an aggressive treatment approach (eg, patients with a high risk of suicide or severely disabled by their symptoms), the most significant predictor of treatment response was early symptom improvement (40% drop in Hamilton scores by 4 weeks), followed by lower levels of baseline anxiety and later age of onset of first episode of depression.[75] No other clinical predictors, including adequacy of previous treatment (as

measured by the antidepressant treatment history form [ATHF] score),[77] race, recurrence, or baseline sleep disturbance reached significance levels (Fig. 2).

For patients requiring a more conservative treatment approach (eg, patients with a history of multiple, unsuccessful, underdosed trials), the most significant predictor of treatment response was again early symptom improvement, followed by baseline anxiety and adequacy of previous antidepressant trials (Fig. 3).

These reports confirmed earlier work on the trajectory of acute response that emphasized that early symptom resolution predicts more stable long-term treatment response.[78,79] Higher levels of acute or chronic stressors, poorer social support, younger age at onset, melancholiform features, older current age, and higher current anxiety also predicted a poorer response profile.[78] The importance of early symptom resolution was further emphasized by the 2006 Maintenance Treatment Trial[16] that noted that patients who needed adjunctive medication in acute treatment to get well also had a more brittle long-term response.

CHALLENGES AND FUTURE DIRECTIONS

Novel Treatment Options

Advances in LLD treatment include novel treatments, personalized treatment (according to depression type, individual characteristics), and strategies to improve access to and delivery of care.[2]

- Novel treatments include transcranial magnetic stimulation (TMS), deep brain stimulation, vagus nerve stimulation (VNS), and magnetic seizure therapy.

TMS has been approved since 2008 as treatment of depression resistant to pharmacotherapy. High-frequency pulse (>1 Hz) repetitive TMS (rTMS) is usually applied to the left dorsolateral prefrontal cortex.[80] A recent randomized, placebo-controlled trial indicated that rTMS may be beneficial for vascular depression (response 39%, remission 27% vs sham 7% and 4% respectively). Subgenual cingulate θ activity predicts treatment response in rTMS in vascular depression.[81]

Deep brain stimulation delivers a continuous train of repetitive, brief small voltage pulses mainly to the subgenual anterior cingulate cortex (ACC), an area that has been associated with treatment-resistant depression.[82] More recent case reports delivered the voltage pulses to either deep brain structures such as nucleus accum-bens and ventral striatum.[83]

VNS was approved for treatment-resistant depression in 2005. The procedure stimulates the left cervical vagus nerve through low-frequency, chronic, intermittent-pulsed electric signals, stimulates areas involved in mood regulation (locus coeruleus, nucleus raphe magnus), and seems to modulate hippocampal neurogenesis.[84] To our knowledge, there are no trials of VNS in LLD.

Several small trials examined the safety and efficacy of magnetic seizure therapy in depression. Its antidepressant effect seems to be less robust than that of ECT.[2]

- Informed/personalized treatment uses neuroimaging techniques such as blood oxygenation level–dependent (BOLD) functional magnetic resonance imaging (fMRI) or diffusion tensor imaging (DTI).

In the last decade, there has been a rapid increase in the availability of magnetic resonance imaging (MRI), and it is likely that, in the near future, MRI accessibility will continue to increase, along with a decrease in scanning costs. If this trend continues, then using MRI to optimize the choice of medications for an individual with depression is possible. The identification of magnetic resonance (MR) markers of treatment response would allow for faster and more efficient trial rather than waiting 3 to 6 weeks to determine whether a new intervention is effective. Several MR markers of treatment response have been identified: lower activation of the rostral ACC at baseline, increased burden of white matter hyperintensities in the frontal regions, and lower fractional anisotropy in frontolimbic areas were associated with poor treatment response in either midlife[85,86] or late-life studies of depression.[87,88]

Pharmacogenetics involves the use of molecular genetic information to assist in the prediction of drug efficacy and drug-induced adverse events. In a heterogeneous disorder such as LLD, pharmacogenetic data could be paramount for the development of individualized treatment approaches.[89] Although the neuroimaging prediction of antidepressant response is not yet refined/cheap enough for clinical applications, genotyping assays are easy to do and their costs have rapidly decreased. Various candidate genes in the serotoninergic system (most notably the serotonin transporter polymorphism) have been associated with treatment response.[90] The serotonin transporter gene (SLC6A4) also influences treatment response variability in LLD, mainly in the initial stages of treatment, through a gene-concentration interaction for SSRIs.[91] In addition, elderly subjects carrying the S allele may be at increased risk of adverse drug reactions and may require a higher initial SSRI plasma concentration to obtain a response.[91,92] Another recent candidate gene (OPRM1, the μ-opioid receptor) has been associated with citalopram response in the STAR*D sample.[93] However, a recent study of 72 candidate genes that also used a genome-wide associate study assessing more than 500,000 SNPs reported modest results.[94] None of the candidate genes provided evidence for association with response to antidepressants.[94]

Sequential treatment:

1. Pharmacotherapy followed by psychotherapy. A recent meta-analysis examined the efficacy of the sequential integration of psychotherapy and pharmacotherapy in reducing the risk of relapse and recurrence in MDD.[95] The pooled risk ratio (RR = 0.79) suggested a relative advantage in preventing relapse and recurrence for the sequential administration of psychotherapy after successful response to acute-phase pharmacotherapy compared with control conditions.[95]
2. ECT followed by pharmacotherapy. Relapse rates after ECT remain high, with virtually all remitted patients relapsing within 6 months of stopping ECT.[55] Most investigators have advocated the use of antidepressants or a combination of antidepressant and mood stabilizer (Li) after completion of ECT.[55] Some experts recommended using antidepressants during ECT to prevent early relapses.[96]

3. rTMS followed by pharmacotherapy. In a recent study, subjects received citalopram (20 mg/d) after either rTMS or sham treatment, with mixed results (of the 12 subjects who responded to rTMS, 9 maintained response and 4 had a relapse of depression).[97]

Various other lines of investigations are being developed. For example, homocysteine has been correlated with increased risk of depression (most likely through the link between the folate/methylation cycles and depression). Lowering homocysteine levels would reduce the incidence and severity of depressive symptoms; a meta-analysis found that older adults with high homocysteine plasma levels have increased risk of depression (odds ratio 1.7).[98]

Health Services Perspectives

The greatest limitation in treatment of LLD concerns treatment access and delivery. In primary care settings, the diagnosis of depression is frequently missed and treatment is often inadequate.[2] Studies such as Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT)[5,99] and Improving Mood Promoting Access to Collaborative Care Treatment (IMPACT)[100] have shown that collaborative care in primary care settings has better outcomes than usual care, and that downstream consequences of inadequately treated depression can be prevented. More importantly, a long-term, developmental perspective on depression across life span is needed.[3] Regarding prevention as protection (prolonging lifespan and healthspan), participation in studies such as PROSPECT[5] have been linked to lower rates of mortality from cancer at 4-year to 5-year follow-up.[3]

Many real-world challenges hinder implementing depression treatment recommendations, such as adequate funds, adequate management of various programs, overcoming barriers in training staff in intervention techniques, ensuring fidelity to established protocols, adequate support to evaluate outcomes, and ensuring accessibility.[101] Partnership among researchers, health care providers, and policy makers is necessary to implement successful treatment protocols for depression in late life.[101]

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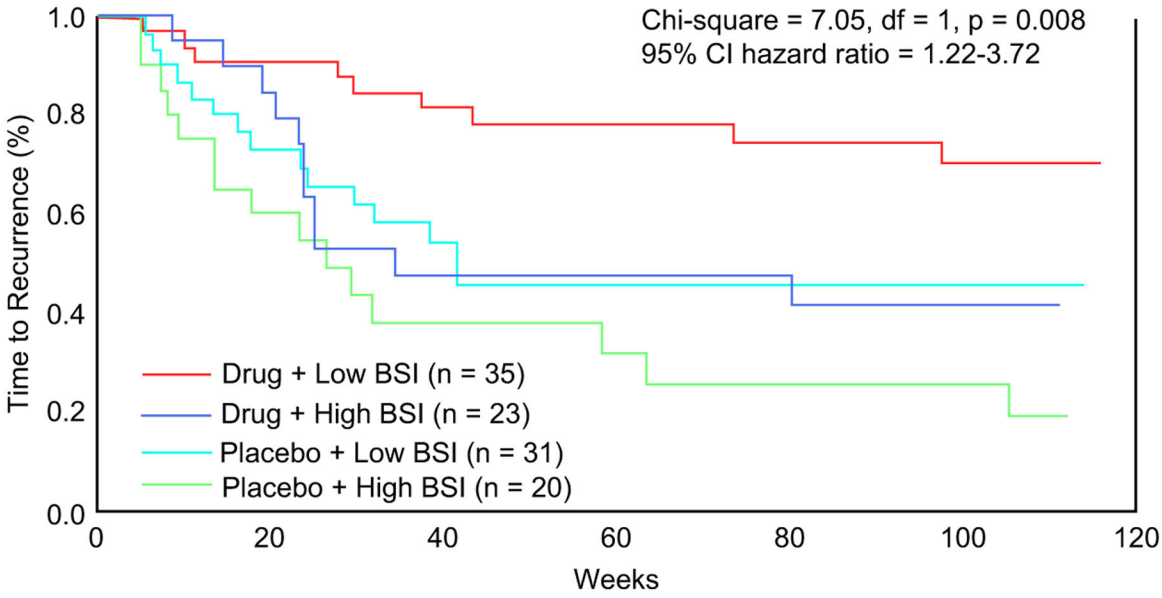

Fig. 1.

Comorbid anxiety symptoms and time to recurrence of late-life depression. (*From* Andreescu C, Lenze EJ, Dew MA, et al. Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: controlled study. Br J Psychiatry 2007;190:347; with permission.)

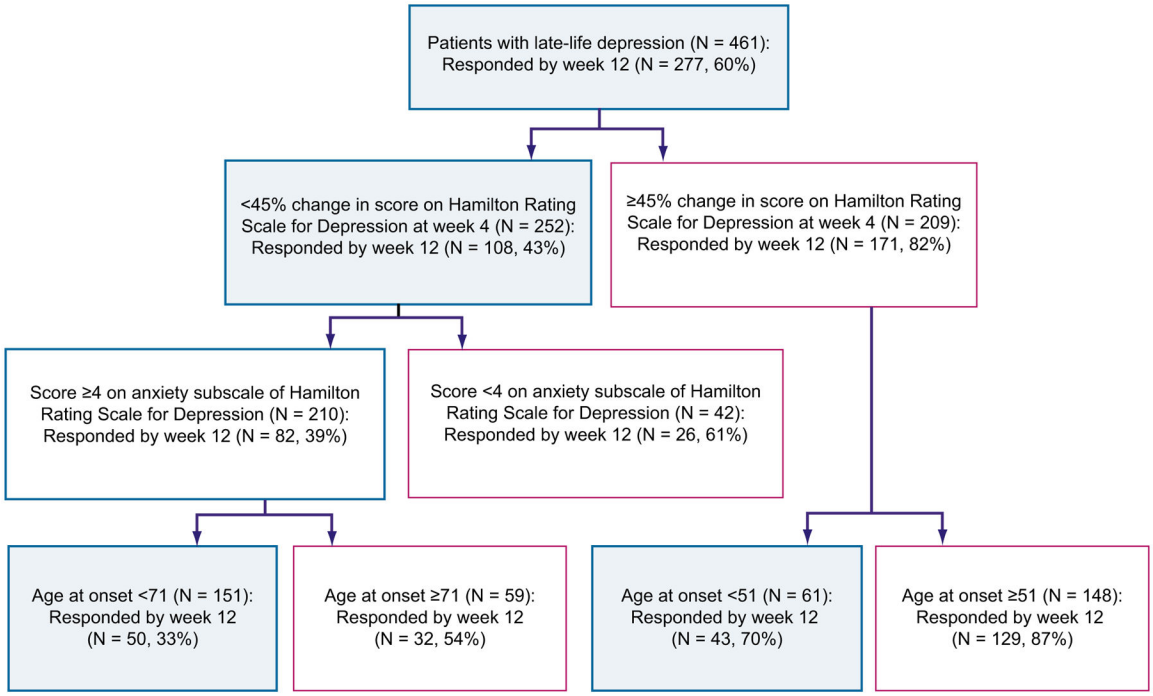

Fig. 2.

Hierarchy of predictors of treatment response with an aggressive treatment approach. Main outcome, full response status at week 12; proportion of responders at 12 weeks, 60%. A change in HRSD score at week 4 of less than 45% from baseline predicts a less-than-half (43%) chance of responding at week 12. For the patients in this group, higher baseline anxiety predicts a 39% chance of responding at week 12. For patients with a higher baseline anxiety, a younger age of onset predicts a 32% chance of responding at week 12. (*From* Andreescu C, Mulsant BH, Houck PR, et al. Empirically derived decision trees for the treatment of late-life depression. Am J Psychiatry 2008;165:859; with permission.)

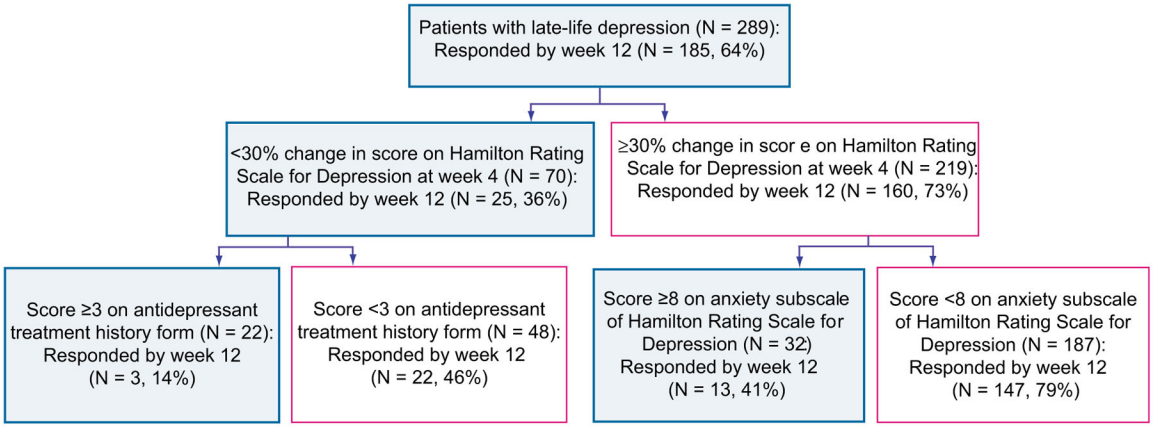

Fig. 3.

Hierarchy of predictors of treatment response with a conservative treatment approach. Main outcome, full response status at week 12; proportion of responders at 12 weeks, 64%. For the ATHF, a score greater than or equal to 3 indicates probably adequate antidepressant treatment history (trial of more than 4 weeks of an antidepressant at an adequate dose); ATHF les than 3 indicates inadequate antidepressant treatment history (trial of less than 4 weeks, or of more than 4 weeks but with an inadequate dose). High anxiety, at least moderate anxiety symptoms; low anxiety, mild or no anxiety symptoms. Change in HRSD at week 4 of less than 30% from baseline predicts a 35% chance of responding at week 12. For those subjects with a change in HRSD at week 4 of less than 30%, a history of at least 1 adequate antidepressant trial predicts a 13% chance of responding at week 12. For those subjects with a change in HRSD at week 4 higher than 30%, the next predictor is baseline anxiety. A higher baseline anxiety score predicts a lower chance of responding at 12 weeks (40%), whereas a lower baseline anxiety score predicts a 79% chance of responding at week 12. (From Andreescu C, Mulsant BH, Houck PR, et al. Empirically derived decision trees for the treatment of late-life depression. Am J Psychiatry 2008;165:860; with permission.)

Table 1

Comparing antidepressants for acute treatment of LLD: duration of treatment

	Primary Outcome Efficacy (Change in HDRS)		Secondary Outcome (Withdrawal Rates)	
Antidepressant Classes Compared	**No. of Trials**	**RR**	**No. of Trials**	**Withdrawal Rates**
	16		26	
TCAs vs SSRIs	9 trials	No difference (RR 1.07, CI 0.94–1.22)	14	SSRI<TCAs (RR 1.36, CI 1.09–1.70)
TCAs vs MAOIs	2 studies	RR 1.16, CI 0.74–1.83	3	ND (RR 0.91, CI 0.64–1.29)
TCAs vs atypicals[a]	4 trials	RR 0.84, CI 0.51–1.38	8	ND (RR 0.96, CI 0.75–1.24)
SSRIs vs MAOIs	1 trial	RR 0.81, CI 0.55–1.20	1	ND (RRs not given)
MAOIs vs atypical	No trial		No trial	
SSRIs vs atypicals	No trial		No trial	

Abbreviations: CI, confidence interval; RR, risk ratio; HDRS, Hamilton Depression Rating Scale; MAOI, monoamine oxidase inhibitors.

[a]Atypical antidepressants: tianeptine, mirtazepine, reboxetine, buspirone, milnaciprin, bupropion.

Data from Mottram P, Wilson K, Strobl J. Antidepressants for depressed elderly. Cochrane Database Syst Rev 2006;1:CD003491.

Table 2

Predictors of treatment response in LLD

Predictors of Treatment Response		Role	Study
Biologic predictors	Serotonin transporter	S allele increases treatment resistance	Lotrich et al,[110] 2008
	REM sleep latency	Decreased REM sleep latency correlates with poor response	Reynolds et al,[102] 1991
	Glucose cerebral metabolism	Reduced glucose metabolism in ACC and mPFC correlated with better response	Smith et al,[103] 1999
	Increased metabolism in ACC	Predicts response to rTMS in vascular depression	Narushima et al,[81] 2010
Clinical predictors	Medical burden	Greater medical burden predicted slower recovery	Dew et al,[41] 2007
	Early symptom improvement	Predicted faster response	Mulsant et al,[104] 2006
	Age of onset of first episode	Younger age at onset predicted poorer response	Dew et al,[78] 1997
	Sleep disturbances	Baseline sleep disturbance predicted poorer response	Reynolds et al,[102] 1991 Dew et al,[78] 1997
	Baseline HDRS scores	Higher score correlated with slower response	Gildengers et al,[105] 2005
	Baseline anxiety	Increased baseline anxiety correlated with slower response	Andreescu et al,[45] 2007
	Suicidal ideation	Baseline suicidal ideation correlated with longer time to response	Szanto et al,[106] 2003
	Response to previous antidepressant treatment	Poor previous antidepressant response correlated with decrease rate of response	Tew et al,[107] 2006
Psychosocial predictors	Social support	Poor social support and poor family support correlated with poor response	Dew et al,[78,108] 1997 Martire et al,[108] 2007
	Social inequalities	Low income correlated with poorer response	Cohen et al,[109] 2006
	Self-esteem	Higher self-esteem correlated with faster response	Gildengers et al,[105] 2005

Abbreviations: ACC, anterior cingulate cortex; HDRS, Hamilton Depression Rating Scale; mPFC, medial prefrontal cortex; REM, rapid eye movement.